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(54) INGESTION OF HYALURONIC ACID FOR IMPROVED JOINT FUNCTION AND HEALTH

(52) U.S. Cl.

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Publication Classification

(57) ABSTRACT

A method is described for relieving joint pain and discomfort in a warm-blooded vertebrate by delivering via oral ingostion a nutritional supplement comprising an effective amount of hyaluronic acid, or a salt or digest thereof, and a nutritionally acceptable carrier. In another embodiment of the present invention, a method is provided for reducing the discomfort of fibromyalgia in a person afflicted with fibromyalgia by delivering via oral ingestion a nutritional supplement comprising an effective amount of hyaluronic acid, or a salt or digest thereof, and a mutritionally acceptable carrier.

INGESTION OF HYALURONIC ACID FOR IMPROVED JOINT FUNCTION AND HEALTH

FIELD OF THE INVENTION

[9001] The present invention relates to a method for relieving joint pain or other discomfort in a warm-blooded vertebrate. More particularly, this invention provides relief of symptoms of arthritic disorders or fibromyalgia by oral ingestion of a composition comprising an effective amount of hyaluronic acid, or a salt or digest thereof.

BACKGROUND AND SUMMARY OF THE INVENTION

[0002] Arthritic disorders, including scute and chronic rheumatoid arthritis and osteoarthritis as well as inflammatory skeletal and musculoskeletal conditions, affect millions of people. It has been estimated that 80% of all individuals over the age of 55 suffer from some form of arthritic disorder. The most common arthritic disorder is osteoarthritis. Osteoarthritis develops gradually over time in many cases. Patients experience alternating periods of mild to moderate pain, stiffness, and swelling of the joint and periods of relatively symptom-free joint activity. Osteoarthritis is characterized by the deterioration of cartilage that covers the ends of bones at a joint, such as the knee or hip. In the healthy joint, cartilage acts as a shock absorber and aids the joint in bearing the stress of physical movement. In addition, synovial joint fluid produced by the synovial membrane lubricates the joint providing a slippery surface over which the bones may move. But as cartilage deteriorates, the bones begin to rub against each other causing joint pain.

[0003] At the same time, the concentration of hydronic sold in the sprovial joint decreases, reducing the Univitation shilling of the synovial joint fluid. Also, joint movement may be restricted as bone ends evode or thicken, and the bones may develop painful outgrowths, or bone spurs, as a casual to this creation or thickening. If fell unteracted, cartilage deterioration can scritching when the point of deformity.

[0004] Current methods of reducing pain in oscoarthritic ionts include treatment with analgesics or anti-inflammatory medications, physical therapy, topical application of hyalurenic acid to the joint, and intra-articular injection of hyalurenic acid directly into the joint. The primary goal of treatment is reduction of pain and maintenance of joint function and strength. Intra-activata injections of hyaluronic acid, known as viscosupplementation, have seen wide for patients who have not resonned well to other therapies.

[9008] Fibromyalgin is a common disabling disorder characterized by chronic insuculoskeletal aches and pain, stiffness, general faligue, and sleep abnormalities. The disorder affects 2-4% of the population and is most frequently found in women between 20 and 50 years old. The exact cause of fibromyalgia remains uncertain, and disgnoss is difficult due to the general nature of the symptoms. Currently, the most effective treatment for fibromyalgia includes a combination of analgesics, sleep nids, exercise programs, relaxation techniques and other measures to reduce muscle tension. These treatments are geared toward improving sleep quality and reducing pain. [9096] The present invention is directed to a method for relieving joint and musculoskeletal discomfort in warmblooded vertebrates comprising the step of delivering to the vertebrate by oral ingestion a composition comprising an effective amount of hyalumoin caid, or a sail or digest thereof, and an acceptable ingestible carrier. The method is used with advantage in treating conditions associated with ostooathritis and for reducing the discomfort of fibromyalgia in a person afflicted with fibromyalgia.

DETAILED DESCRIPTION OF THE INVENTION

[6007] Hyaluronic acid is a mucupolysaccharide that is bound in joint tissue and in the viterous humor of the eye. Hyaluronic acid functions as a protective coating and a lubricant for soft tissue and joints, and additionally, helps maintain the structural integrity of soft tissue. In association with protein, hyaluronic acid binds water in the intercellular spaces and holds cells together in a jellylike matrix. This jellylike matrix provides lubrication and shock absorption throughout the body.

[9008] In the healthy kince joint, hyaluronic acid is present both in the cartilage covering the ends of bone and in the synovial joint fluid. Hyahuronic acid is usually found as part of proteoglycan aggregates in cartilage, where it height cartilage withstand forces of weight bearing and joint movement. Hyaluronic acid is also a major component of synovial joint fluid. The synovial joint fluid provides bufferiacion for the cartilage against the lining of the joint and may provide some additional shock-absorption value.

[0009] Hyaluronic acid is commercially available and is prepared from the intracellular matrices of animal connective tissue, such as rooster combs and bovine tissue sources, mammalian umbilical cords, and bacterial organisms such as streptococcus receptiones. Its molecular weight ranges from about 50000 to about 8x10.6 Daltons depending on source and method of isolation. Treatment with hyaluronidases can be used to provide hydrolysates of reduced molecular weight range.

[0010] The present method provides relief from joint pain and musculoskeletal discomfort in a warm-blooded vertexe saffering from an arthritic condition or flormyalgia. An arthritic condition includes acute and chrome rheumstoid arthritis and ostocarthritis, as well as inflammatory conditions involving skeletal conditions.

[9011] In accordance with the present invention, a method is provided for relieving joint or musculoscleid pain or discomfort in a warm-blooded vertebrate comprising delivering to the vertebrate by oral ingestion a composition comprising an effective amount of byahronic acid, or a salt or digest thereof, and a nutritionally acceptable carrier. An "effective amount" as used herein refers to the smount of hyahronic acid which, upon oral administration, provides relief of joint pain or discountort. The effective amount of hyahronic acid, or a salt or digest thereof, is from about 0.1 µg/kg to about 400 µg/kg of body weight per dose. The awarn-blooded vertebrate may be a human, or an equine, canine, or feline species. In ore embodiement the method is chemically a person affacted with osescont-herits:

[0012] In another embodiment the method is used for reducing the discomfort of fibromyalgia. The hyaluronic acid, salt or digest is orally ingested with a acceptable carrier, typically an aqueous beverage or food product. Preferably, the hyaluronic acid, salts or hydrolysates for use in the present invention is formulated into a liquid aqueous concentration, for example, a dietary supplement formulation, which is diluted in portions and mixed with food, water, or other beverages for oral ingestion. Alternatively the hyshuronic acid, salt, or hydrolysate can be packaged in individual solid or liquid doses, for instance in capsules or gel seals. The concentrate can contain about 1 to about 10 mg of hyaluronic acid, its salt or hydrolysate per milliliter of concentrate. In one embodiment a dose is administered by combining 7 to 10 drops of the concentrate in a cold beverage which is consumed on conjunction with a meal, for example.

EXAMPLES

Example 1

Oral Ingestion of Hyaluronic Acid By Patients Suffering From Osteoarthritis

[9013] A study involving sixty-seven patients suffering term enterarhitis was understate to determine the effectiveness of oral ingestion of hyaluronic acid. Each patient received 1-4 mg of hyaluronic acid by oral ingestion administration 1 to 4 times a day over periods ranging from about 4 to about 2 weeks, during which period the patients' subjective pain feeling was reported. Twenty-sime patients acid, and additionally reported increased range of motion. Twenty-four patients reported (35.8%) some degree of pain relief and some increased range of motion. Fourteen patients reported (35.8%) some degree of pain relief and some increased range of motion. Fourteen patients reported of some of motion.

Example 2

Oral Ingestion of Hyaluronic Acid by Patients Afflicted With Fibromyalgia

[0014] Another study involving thirty-five human patients suffering pain and discomfort associated with fibromyalgia was undertaken to evaluate the effectiveness of oral ingestion of hyaluronic acid. Each patient received about 1 to about 6 mg of hyaluronic acid by oral ingestion administration of concentrate diluted into beverages or food. Over a

treatment period of about 1 to about 14 monits, the patients' subjective pain feeling was reported. Twenty-one patients reported no pain after hyakuronic acid therapy. Six patients (17.198) reported some (60%) degree of pain relief. Eight patients reported no change in the amount of pain they felt.

1. A method for relieving joint pain or other discomfort in a warm-blooded verterate comprising the step of delivering to said vertebrate by oral ingestion a composition comprising an effective amount of hyaluronic acid, or a salt or digest thereof, and a food acceptable carrier.

The method of claim 1 wherein the nutritional supplement consists essentially of said hyaluronic acid, or a salt or

digest thereof, and the carrier therefor.

The method of claim 1 further comprising the step of adding the hysluronic acid, or a sail or digest thereof, to the carrier, and wherein the carrier comprises food or water.

 The method of claim 1 wherein the nutritional supplementations.

ment is provided in capsule form.

5. The method of claim 1 wherein the effective amount of hydranic acid, or a salt or digest thereof, is from about 0.1 μ g to about 400 μ g/kg of body weight.

 The method of claim 1 wherein the warm-blooded vertebrate is a human, or an equine, canine, or feline species.

7. The method of claim 1 wherein the joint pain is the result of an arthritic condition.

8. The method of claim 1 wherein the joint pain is the

 The method of claim 1 wherein the joint pain is the result of an inflammatory condition involving skeletal or musculoskeletal structures.

9. A method for reducing discomfort of libromyalgia in a person afficied with fibromyalgia comprising the step of delivering to said person by oral ingestion a mutritional supplement comprising an effective amount of hyaluronic acid, or a salt or digest thereof, and a nutritionally acceptable carrier.

10. The method of claim 9 wherein the nutritional supplement consists essentially of said hydratonic acid, or a sait or digest thereof, and the carrier therefor.

11. The method of claim 9 further comprising the step of adding the hyaluronic acid, or a salt or digest thereof, to the carrier, and wherein the carrier comprises food or water.
12. The method of claim 9 wherein the nutritional supple.

ment is provided in capsule form.

13. The method of claim 9 wherein the effective amount

13. The method of claim 9 wherein the effective amount of hyaluronic acid, or a salt or digest thereof, is from about 0.1 μg to about 400 μg/kg of body weight.

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- (54) INGESTION OF HYALURONIC ACID FOR IMPROVED JOINT FUNCTION AND HEALTH
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- (*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.
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424/442, 451, 452; 514/825

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(57) ABSTRACT

Methods are described for relieving discomforts associated with osteoanthritis or fibromyalgia. The methods comprise the step of delivering by oral ingestion a nutritional supplement consisting essentially of an effective amount of hyabinonic acid, or a salt or digest thereof, and a food acceptable carrier, wherein the effective amount of hyabinoric acid, or a salt or digest thereof, is from about 0.1 µg to about 400 µg/kg of body weight.

7 Claims, No Drawings

INGESTION OF HYALL/RONIC ACID FOR IMPROVED JOINT FUNCTION AND HEALTH

FIELD OF THE INVENTION

The present invention relates to a method for relieving joint pain or other discomfort in a warm-blooded vertebrate. More particularly, this invention provides relief of symptoms of arthritic disorders or fibromyalgia by oral ingestion 10 of a composition comprising an effective amount of hyaluronic acid, or a salt or digest thereof.

BACKGROUND AND SUMMARY OF THE INVENTION

Arthritic disorders, including acute and chronic rheumatoid arthritis and ostcoarthritis as well as inflammatory skeletal and musculoskeletal conditions, affect millions of people. It has been estimated that 80% of all individuals over the age of 55 suffer from some form of arthritic disorder. The most common arthritic disorder is osteoarthritis. Osteoarthritis develops gradually over time in many cases. Patients experience alternating periods of mild to moderate pain, stiffness, and swelling of the joint and periods of relatively symptom-free joint activity. Ostcoarthritis is characterized 25 by the deterioration of cartilage that covers the ends of bones at a joint, such as the knee or hip. In the healthy joint, cartilage acts as a shock absorber and aids the joint in bearing the stress of physical movement. In addition, synovial joint fluid produced by the synovial membrane lubricates the joint providing a slippery surface over which the bones may move. But as cartilage deteriorates, the bones begin to rub against each other causing joint pain.

At the same time, the concentration of hyaluronic soid in the synovial joint decreases, reducing the lubrication ability of the synovial joint fluid. Also, joint movement may be restricted as bone ends crode or thicken, and the bones may develop painful outgrowths, or bone spurs, as a result of this erosion or thickening. If left untreated, cartilage deterioration can seriously weaken the joint, possibly to the point of

Current methods of reducing pain in osteoarthritic joints include treatment with analgesics or anti-inflammatory ronic acid to the joint, and intra-articular injection of hyaluronic acid directly into the joint. The primary goal of treatment is reduction of pain and maintenance of joint function and strength. Intra-articular injections of hyaluronic acid, known as viscosupplementation, have seen wide use 50 for patients who have not responded well to other therapies.

Fibromyalgia is a common disabling disorder characterized by chronic musculoskeletal aches and pain, stiffness, general fatigue, and sleep abnormalities. The disorder affects 2-4% of the population and is most frequently found in ss women between 20 and 50 years old. The exact cause of fibromyalgia remains uncertain, and diagnosis is difficult due to the general nature of the symptoms. Currently, the most effective treatment for fibromyalgia includes a combination of analgesics, sleep aids, exercise programs, relax- 60 ation techniques and other measures to reduce muscle tension. These treatments are geared toward improving sleep quality and reducing pain.

The present invention is directed to a method for relieving tebrates comprising the step of delivering to the vertebrate by oral ingestion a composition comprising an effective

amount of hyaluronic acid, or a salt or digest thereof, and an acceptable ingestible carrier. The method is used with advantage in treating conditions associated with osteoarthritis and for reducing the discomfort of fibromyalgia in a 5 person afflicted with fibromyalgia.

DETAILED DESCRIPTION OF THE INVENTION

Hyaluronic acid is a mucopolysaccharide that is found in joint tissue and in the vitreous humor of the eye. Hyaluronic acid functions as a protective coating and a lubricant for soft tissue and joints, and additionally, helps maintain the structural integrity of soft tissue. In association with protein, hyaluronic acid binds water in the intercellular spaces and 15 holds cells together in a jellylike matrix. This jellylike matrix provides lubrication and shock absorption throughout the body.

In the healthy knee joint, hyaluronic acid is present both in the cartilage covering the ends of bone and in the synovial joint fluid. Hyaluronic acid is usually found as part of proteoglycan aggregates in cartilage, where it helps cartilage withstand forces of weight bearing and joint movement. Hyaluronic acid is also a major component of synovial joint fluid. The synovial joint fluid provides lubrication for the cartilage against the lining of the joint and may provide some additional shock-absorption value.

Hyaluronic acid is commercially available and is prepared from the intracellular matrices of animal connective tissue. such as rooster combs and bovine tissue sources, manimalian umbilical cords, and bacterial organisms such as streptococcus zoepidicus. Its molecular weight ranges from about 50000 to about 8×106 Daltons depending on source and method of isolation. Treatment with hyaluronidases can be used to provide hydrolysates of reduced molecular weight

The present method provides relief from joint pain and musculoskeletal discomfort in a warm-blooded vertebrate suffering from an arthritic condition or fibromyalgia. An arthritic condition includes acute and chronic rheumatoid arthritis and osteoarthritis, as well as inflammatory conditions involving skeletal conditions and musculoskeletal con-

In accordance with the present invention, a method is medications, physical therapy, topical application of hyalu- 45 provided for relieving joint or musculoskeletal pain or discomfort in a warm-blooded vertebrate comprising delivering to the vertebrate by oral ingestion a composition comprising an effective amount of hyaluronic acid, or a salt or digest thereof, and a nutritionally acceptable carrier. An "effective amount" as used herein refers to the amount of hyaluronic acid which, upon oral administration, provides relief of joint pain or discomfort. The effective amount of hyaluronic acid, or a salt or digest thereof, is from about 0.1 μα/kg to about 400 μg/kg of body weight per dose. The warm-blooded vertebrate may be a human, or an equine, canine, or feline species. In one embodiment the method is used to reduce joint pain a a person afflicted with ostcoarthritis.

In another embodiment the method is used for reducing the discomfort of fibromyalgia. The hyaluronic acid, salt or digest is orally ingested with a acceptable carrier, typically an aqueous beverage or food product. Preferably, the hyaluronic acid, salts or hydrolysates for use in the present invention is formulated into a liquid aqueous concentration, joint and musculoskeletal discomfort in warm-blooded ver- 65 for example, a dietary supplement formulation, which is diluted in portions and mixed with food, water, or other beverages for oral ingestion. Alternatively the hyaluronic acid, salt, or hydrolysate can be packaged in individual solid or figuid doses, for instance in cansules or gel seals. The concentrate can contain about 1 to about 10 mg of hyaluronic acid, its salt or hydrolysate per milliliter of concentrate. In one embodiment a dose is administered by combining 7 to 10 drops of the concentrate in a cold beverage which is consumed on conjunction with a meal, for example.

EXAMPLES

Example 1

Oral Ingestion of Hvaluronic Acid By Patients Suffering From Osteoarthritis

A study involving sixty-seven patients suffering from 15 about 0.1 µg to about 400 µg/kg of body weight. osteoarthritis was undertaken to determine the effectiveness of oral ingestion of hyaluronic acid. Each patient received 1-4 mg of hyaluronic acid by oral ingestion administration 1 to 4 times a day over periods ranging from about 4 to about 2 weeks, during which period the patients' subjective pain 20 ment is provided in capsule form. feeling was reported. Twenty-nine patients (43.3%) reported no pain after oral ingestion of hyaluronic acid, and additionally reported increased range of motion. Twenty-four patients reported (35.8%) some degree of pain relief and some increased range of motion. Fourteen patients reported 25 no change in the amount of pain they felt.

Example 2

Oral Ingestion of Hyaluronic Acid by Patients Afflicted With Fibromyalgia

Another study involving thirty-five human patients suffering pain and discomfort associated with fibromyalgia was undertaken to evaluate the effectiveness of oral ingestion of 35 ment is provided in capsule form. hyaluronic acid. Each patient received about I to about 6 mg of hyaluronic acid by oral ingestion administration of con-

centrate diluted into beverages or food. Over a treatment period of about 1 to about 14 months, the natients' subjective pain feeling was reported. Twenty-one patients reported no pain after hyahuronic acid therapy. Six patients (17.1%) reported some (60%) degree of pain relief. Eight patients reported no change in the amount of pain they felt. What is claimed is:

1. A method for relieving joint pain or other discomforts associated with osteoarthritis in a warm-blooded vertebrate 10 comprising the step of delivering to said vertebrate by oral ingestion a nutritional supplement consisting essentially of an effective amount of hyaluronic acid, or a salt or digest thereof, and a food acceptable carrier, wherein the effective amount of hyaluronic acid, or a salt or digest thereof, is from

2. The method of claim 1 further comprising the step of adding the hyaluronic acid, or a salt or digest thereof, to the carrier, and wherein the carrier comprises food or water.

3. The method of claim I wherein the nutritional supple-

4. The method of claim 1 wherein the warm-blooded vertebrate is a human, or an equine, canine, or feline species.

5. A method for reducing discomfort of fibromyalgia in a person afflicted with fibromyalgia comprising the step of delivering to said person by oral ingestion a nutritional supplement consisting essentially of an effective amount of hyaluronic acid, or a salt or digest thereof, and a patritionally acceptable carrier, wherein the effective amount of hvaluronic acid, or a salt or digest thereof, is from about 0.1 µg 30 to about 400 µg/kg of body weight.

6. The method of claim 5 further comprising the step of adding the hysluronic acid, or a salt or digest thereof, to the carrier, and wherein the carrier comprises food or water.

7. The method of claim 5 wherein the nutritional supple-

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(54) INGESTION OF HYALURONIC ACID FOR IMPROVED JOINT HEALTH

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(21) Appl. No.: 10/629,880

(22) Filed: Jul. 29, 2003

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Publication Classification

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(57) ABSTRACT

Methods and compositions are described for relieving joint pain and discomfort in a warm-blooded vertebrate by delivering via oral ingestion a nutritional supplement comprising an effective amount of byaluronic acid, or a salt or digest thereof, and a nutritionally acceptable carrier.

CROSS-REFERENCE TO RELATED APPLICATION

[0001] This application is a continuation-in-part of U.S. patent application Ser. No. 09/860,425, filed May 18, 2001, herein incorporated by reference.

FIELD OF THE INVENTION

[0002] The present invention relates to a method for relieving joint pain or other discomfort in a warm-blooded vertebrate. More particularly, this invention provides relief of symptoms of arthritic disorders or fibromyalgia by oral ingestion of a composition comprising an effective amount of hvaluronic acid, or a salt or disest thereof.

BACKGROUND AND SUMMARY OF THE INVENTION

[0003] Arthritic disorders, including acute and chronic theuntoid arthritis and ostoorathritis as well as inflammatory skeletal and museuloskeletal conditions, affect millions of people. It has been estimated that 80% of all individuals over the age of 55 sulfor from some form of arthritis obsorders nows common arthritic disorders to sotoconthritis. Ostoorathritis develops gradually over time in many cases. Patients experience afternating periods of mild to moderate pain, stiffness, and swelling of the joint and periods of relatively swrptom-free joint activity.

[0004] Osteoarthritis is characterized by the deterioration of cartilage that covers the ends of bones at a joint, such as the knee or hip. In the healthy joint, cartilage acts as a shock absorber and aids the joint in bearing the stress of physical movement. In addition, synovial joint fluid produced by the synovial membrane lubricates the joint providing a slippery surface over which the bones may move. But as cartilage deteriorates, the bones begin to rub against each other causing joint pain. At the same time, the concentration of hyaluronic acid in the synovial joint decreases, reducing the lubrication ability of the synovial joint fluid. Also, joint movement may be restricted as bone ends crode or thicken, and the bones may develop painful outgrowths, or bone spurs, as a result of this erosion or thickening. If left untreated, cartilage deterioration can seriously weaken the joint, possibly to the point of deformity.

[9005] Current methods of reducing pain in osteoarthritic joints include treatment with analgesies or anti-inflammatory medications, physical therapy, topical application of hyabronic acid to the joint, and intra-articular injection of hyabronic acid directly into the joint. The prinary goal of treatment is reduction of pain and maintenance of joint function and strength. Intra-articular injections of hyabronic acid, known as viscosupplementation, have seen wide use for patients who have not responded well to other thorapies.

[0006] Fibromyalgia is a common disabling disorder characterized by chronic musculoskelat a debts and pain, siffiness, general fatigue, and sleep abnormalities. The disorder affects 2-4% of the population and is most frequently found in women between 20 and 50 years old. The exact cause of fibromyalgia remains uncertain, and diagnosis is difficult due to the general nature of the symptoms. Currently, the most effective treatment for fibromyslgia includes a combination of analgesics, sleep aids, exercise programs, relaxation techniques and other measures to reduce muscle tension. These treatments are geared toward improving sleep quality and reducing pain.

[0007] Rheumatoid Arthritis is a chronic, systemic, inflammatory disease that chiefly affects the synovial membranes of multiple joints in the body. Rheumatoid arthritis is considered to be an autoimmune disease, in which the patient has remissions and exacerbations of the symptoms. Joints that are actively involved with the disease are usually tender, swollen, and likely demonstrate reduced motion. Several different classes of drugs are often use to treat patients with rheumatoid arthritis, including analgesies to control pain, corticosteroids, urie acid-lowering drugs, immunosuppressive drugs, mosteroidal antiinflammatory drugs, and disease-modifying autirheumatic drugs. Many patients with rheumatoid arthritis also note a decrease in their symptoms after application of heat.

[9008] The present invention is directed to a method for relieving joint and misculoskeletal discomfort in warmblooded vertebrates comprising the step of delivering to the vertebrate by oral ingestion a composition comprising an effective amount of hyalumoria caid, or a salt or digest thereof, and an acceptable ingestible carrier. The method is used with advantage in treating conditions associated with arthritis and for reducing the discomfort of fibromyalgia in a person afflicted with fibromyalgia.

[0009] Additional features of the present invention will become apparent to those skilled in the art upon consideration of the following detailed description of the preferred embodiments.

DETAILED DESCRIPTION OF THE INVENTION

[0010] Hyaluronic acid is a mucopolysaccharde that is found in joint issue and in the vitrous lumon of the eye. Hyaluronic acid functions as a protective coating and a lubricant for soft issue and joints, and additionally, leips maintain the structural integrity of soft tissue. In association with protein, hyaluronic acid binds water in the intercellular spaces and holds cells together in a jelly like matrix. This jellylike matrix provides lubrication and shock absorption throughout the body.

[0011] In the healthy knee joint, hyaluronic acid is present both in the cartilage covering the ends of bone and in the synovial joint fluid. Hyaluronic acid is usually found as partiage withstand forces of weight bearing and joint movement. Hyaluronic acid is also a major component of synovial joint fluid. The synovial joint fluid provides butiestication for the cartilage against the liming of the joint and may provide some additional shock-absorption value.

[0012] Hyaluronic acid is commercially available and is prepared from the intracellular matrices of animal connective tissue, such as roosler combs and bovine tissue sources, mammalian umbilical cords, and bacterial organisms such as steptococcus zwepidicus. Its molecular weight ranges from about 50000 to about 8x10⁸ Daltons depending on source and method of losalton. Textment with bysulronidases can be used to provide hydrolysates of reduced molecular weight range. [0013] The present method provides relief from joint pain and musculoskeletal discomfort in a warm-blooded vertebrate suffering from an arthritic condition or fibromyalgia. An arthritic condition includes acute and chronic theumatoid arthritis and ossocrathritia, as well as inflammatory conditions involving skeletal conditions and musculoskeletal conditions.

[9014] In accordance with the present invention, a method is provided for relieving joint or musculoskeltal pain or discomfort in a warm-blooded vertebrate comprising delivering to the vertebrate by or all ingestion a composition comprising an effective amount of hyaluronic acid, or a salt or digest thereof, and a nutritionally acceptable carrier. An "effective amount" as weed herein refers to the amount of hyaluronic acid, or a salt or digest thereof, is from about 0.1 paging to about 400 paging of body weight per dose. The warm-blooded vertebrate may be a human, or an equine, causing, or faine species, in one emboliment the method with the state of the composition of the properties of

[0015] In another embodiment the method is used for reducing the discomfort of fibromyalgia. The hyaluronic acid, salt or digest is orally ingested with an acceptable carrier, typically an aqueous beverage or food product. Preferably, the hyaluronic acid, salts, or hydrolysates for use in the present invention are formulated into a liquid aqueous concentration, for example, a distary supplement formulation, which is diluted in portions and mixed with food, water, or other beverages for oral ingestion. Alternatively the hyaluronic acid, salt, or hydrolysate can be packaged in individual solid or liquid doses, for instance in capsules or gel seals. The concentrate can contain about 1 to about 10 mg of hyaluronic acid, its salt, or hydrolysate per milliliter of concentrate. In one embodiment a dose is administered by combining 7 to 10 drops of the concentrate in a cold beverage which is consumed on conjunction with a meal, for example.

EXAMPLES

Example 1

Oral Ingestion of Hyaluronic Acid by Patients Suffering from Osteoarthritis

[9016] A study involving sixty-seven patients sufficing from osteoarthritis was undertaken to determine the effectiveness of crat ingestion of hyaluronic said. Each patient received 1-4 mg of hyaluronic said. Pack patient istration 1 to 4 times a day over periods ranging from shout 4 to about 2 weeks, during which period the patients' subjective pain feeling was reported. Twenty-rine patients (24.3%) reported no pain after oral ingestion of hyaluronic acid, and additionally reported increased range of motion. Twenty-from patients reported (25.8%) some degree of pain relief and some increased range of motion. Fourteen patients reported (25.8%) some degree of pain relief and some increased range of motion. Fourteen patients reported (25.8%) some degree of pain relief and some increased range of motion.

Example 2

Oral Ingestion of Hyaluronic Acid by Patients Afflicted with Fibromyalgia

[0017] Another study involving thirty-five human patients suffering pain and discomfort associated with fibromyalgia

was undertaken to evaluate the effectiveness of oral ingestion of hydromic acid. Each patient received about 1 to about 6 mg of hydromic acid by oral ingestion administration of concentrate diluted into bevergess or food. Over a treatment period of about 1 to about 14 months, the patients' subjective pain feeling was reported. Twenty-one patients reported on pain after hydromic acid therapy. Six patients (17.1%) reported some (60%) degree of pain relief. Eight patients reported no change in the amount of pain they felt.

Example 3

Oral Ingestion of Hyaluronic Acid by Patients Afflicted with Rheumatoid Arthritis

[0018] Another study involving seventeen human patients suffering pain and discomfort associated with thenmatoid anhritis was undertaken. Each patient received about 1 mg of an oral hyaluronic said solution for a period of 30 days. Each patient was saked to evaluate his or her subjective pain feeling and report the score on a scale of 0 to 10, wherein 0 means no pain and/or stiffness whatsoever and 10 means worst imaginable pain and/or stiffness. Prior to the start of the study, the patients reported as follows:

| 1 patient reported | 7 | |
|---------------------|----|--|
| 8 patients reported | 8 | |
| 4 patients reported | 9 | |
| 2 patients reported | 10 | |

[0019] for an average of 8.47. At the completion of the 30-day study, the patients responded as follows:

| 3 patient reported | n | |
|---------------------|----|--|
| I patient reported | 1 | |
| 3 patients reported | 2 | |
| 7 patients reported | 3 | |
| 2 patients reported | 7 | |
| 1 patient reported | 10 | |

[9020] for an average of 3.47, which is considerably lower than the pain reported prior to treatment. Two of the seventeen patients did not respond to the questionnaire.

[9021] Given that oral ingestion of byshronic acid reduced join pain and other discomforts due to osteoarthritis, fibromyalgia, and rheumatoid arthritis, it is expected that oral ingestion of hyaluronic acid would reduce joint pain and stiffness resulting from a variety of conditions.

[9022] Although the invention has been described in detail with reference to certain preferred embodiments, those skilled in the art will recognize that the invention can be practiced with variations and modifications within the scope and spirit of the invention as described and defined in the following claims.

1. A method for relieving joint pain or other discomforts associated with joint disorders in a warm-blooded vertebrate comprising the step of delivering to said vertebrate by oral ingestion a nutritional supplement consisting essontially of an effective amount of hyahuronic acid, or a said or digest thereof, and a food acceptable cerrier, wherein the effective amount of hysturonic acid, or a salt or digest thereof, is from about 0.1 μg to about 400 $\mu g/kg$ of body weight

- The method of claim 1 further comprising the step of adding the hyaluronic acid, or a salt or digest thereof, to the carrier, and wherein the carrier comprises food or water.
- The method of claim 1 wherein the nutritional supplement is provided in capsule form.
- 4. The method of claim 1 wherein the warm-blooded vortebrate is a human, or an equine, canine, or feline species.
 5. The method of claim 1 wherein the joint pain is the result of an arthritic condition.
- The method of claim 5 wherein the arthritic condition is selected from the group consisting of osteoarthritis and rheumatoid arthritis.
- The method of claim 1 wherein the joint pain is the result of an inflammatory condition involving skeletal or musculoskeletal structures.
- 8. A nutritional supplement consisting essentially of an effective amount of hyaluronic acid, or a salt or digest thereof, and a food acceptable carrier, the nutritional supplement provided in an orally ingestible dosage form.
- 9. The nutritional supplement of claim 8 wherein the effective amount of hyaluronic acid is 1 to 6 mg.
- 10. The nutritional supplement of claim 8 wherein the orally ingestible dosage form is a capsule or get seal.

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PROVISIONAL APPLICATION COVER SHEET This is a request for filing a PROVISIONAL APPLICATION under 37 C.F.R. § 1.53(b)(2).

Attorney Docket Number: 2781.01US01

INVENTOR(S) / APPLICANT(S) MIDDLE INITIAL.

RESIDENCE (City and Either State or Foreign Country)

Lexington, Kentucky

TITLE OF INVENTION (280 characters max)

CHONDROPROTECTIVE/RESTORATIVE COMPOSITIONS AND METHODS THEREOF

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Scott

| ENCLOSED APPLICATION PARTS (check all that apply) | | | | | | | | | | |
|---|---------------------------------------|-----------|-----------|---|------------------------|--|--|--|--|--|
| Specification Drawings | Number of Pages: Number of Sheets: | 37 |] |] | Small Entity Statement | | | | | |
| | | METHOD OF | A MAKENIT | | | | | | | |

A check in the amount of \$0.00 is enclosed to cover the provisional application filing fee. The Commissioner is hereby authorized to charge any additional filing fees and/or to credit any overpayment to our Deposit Account Number 16-0631.

The invention was made by an agency of the U.S. Government or under a contract with an agency of the U.S. Government. [X] No.

Yes. The name of the U.S. Government agency and the Government contract number are:

Respectfully submitted.

Date: October 3, 2000

John F. Bolan

Registration, No. 45,382

PROVISIONAL APPLICATION FILING ONLY

CERTIFICATE OF EXPRESS MAIL

"Express Mail" mailing label number: EL595680945US. Date of Deposit: October 3, 2000. I hereby certify that this paper is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 C.F.R. § 1,10 on the date indicated above and is addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231.

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CHONDROPROTECTIVE/RESTORATIVE COMPOSITIONS AND METHODS THEREOF

Provisional Application

BACKGROUND OF THE INVENTION

The present invention, which goes by the name Chondrogen EQ, was initially formulated for the growing horse and equine athlete. It is the most unique chondroprotective / restorative agent available. In one embodiment, the molasses flavored oral paste provides a practical, efficient, and effective means of administration orally or top dressing feed. When added to the feed, this embodiments molasses base binds to the feed to insure total consumption. When necessary, an easy measure dose can be administered orally. This highly palatable formulation is the first to combine high levels of Glucosamine sulfate (GS) with Chondroitin sulfate (CS) and Hyaluronic Acid (HA) in an easy to absorb, low molecular weight formula. It has also been shown that liquid or paste forms are more readily absorbed than encapsulated or powder forms. A chondroprotective / restorative agent should enhance chondrocyte synthesis, increase synthesis of hyaluronic acid, inhibit enzymes that degrade cartilage, and reduce pain and synovitis. It must also slow down or reverse progression of the disease. The present invention, with it's unique combination of GS, CS, and HA is the closest yet to satisfying these criteria.

These three substances are the three connective tissue molecules needed to rebuild and synthesize new tissue.

Connective tissue is comprised mainly of collagen and proteglycans. Proteoglycans provide the framework for collagen and hold water, enhancing the flexibility and resistance to compression needed to counteract physical stress. The building blocks for all proteglycans are amino sugars. Glucosamine is the building block needed as the precursor for all subsequent amino sugar synthesis. The formation of N-acetylglucosamine, chondroitin sulfate, and hyaluronic acid require glucosamine for their synthesis. In fact, glucosamine makes up 50% of the hyaluronic acid molecule.

Glucosamine sulfate along with Chondroitin sulfate have become very popular supplements administered in the treatment of degenerative joint disease. Recent studies have questioned whether the combination produces better results than Glucosamine sulfate alone. Also there is much debate over which glucosamine salt is preferred. Embodiments of the present invention utilize Glucosamine sulfate as it's source of Glucosamine. Most of the past and present research has been performed on the sulfated form. There is evidence that suggests that a component of the activity of GS and CS is related to the sulfate residues found in these compounds. Sulfur is an essential nutrient for the stabilization of the connective tissue matrix. It has been proposed that the sulfate molecules of GS and CS contribute to the therapeutic benefits of these compounds in degenerative joint disease. If this is true, it would suggest that GS, as opposed to N-acetylglucosamine and glucosamine HCl, is the best form of glucosamine supplementation. Recently, it has been shown that high-dose glucosamine may provide rapid symptomatic benefit and in the longer term aid the repair of damaged cartilage. The high does of glucosamine non only promotes synthesis of cartilage proteoglycans, but stimulates synovial production of hyaluronic acid. This would explain the anecdotal reports that a high does of glucosamine is beneficial.

SUMMARY AND DETAILED DESCRIPTION OF INVENTION

As previously explained, the present invention comprises a highly palatable formulation, which is the first to combine high levels of Glucosamine sulfate (GS) with Chondroitin sulfate (CS) and Hyaluronic Acid (HA) in an easy to absorb, low molecular weight formula.

Glucosamine, which is formed in the body as glucosamine 6-phosphate is the most fundamental building block required for the biosynthesis of the classes of compounds such as glucolipids, glycoproteins, glycosamineoglycans, hyaluronate, and proteoglycans. Directly or indirectly, glucosamine plays a role in the formation of articular surfaces, tendons, ligaments, synovial fluid, skin, bone, heart valves, blood vessels and mucus secretions of the digestive, respiratory, and urinary tracts. Glucosamine sulfate is greater than 90% absorbed and is quickly incorporated into articular cartilage following oral administration.

In one study, no LD50 was established for Glucosamine sulfate since even at very high levels (5000 mg/kg orally) there was no mortality in mice and rats. While treatment with GS does not produce the initial dramatic reductions in pain normally associated with NSAIDs, it's ability to reduce pain is consistent and progressive throughout the course of it's administration, resulting in a long-term improvement in the condition. Glucosamine is a small molecule and is very soluble in water.

Chondroitin Sulfate achieves benefits much more slowly than glucosamine. Chondroitin bioavailability following oral administration is around 15%. Because of its lower availability, the time needed to see a clinical response is lengthened. Chondroitin improves joint fluidity by drawing water to the cartilage tissue. When this water is drawn into the cartilage, it is

accompanied by nutrients which are supplied to the cartilage. Additionally, Chondroitin helps fight enzymes that inhibit transportation of nutrients into these tissues as it prevents other enzymes from tearing down cartilage tissue. Furthermore, Chondroitin, like Glucosamine, promotes the product of key cartilage components such as proteoglycans and it also prevents abnormal cell death.

Hyaluronic acid is a naturally occurring glycosaminoglycan. HA is a ubiquitous in the organism, with the highest concentration found in soft connective tissue and joint fluid. It is a constituent of the intercellular matrix of connective tissue that exists in almost all vertebrates. It plays an important role in a number of physiological functions, including protection and lubrication of cells, maintenance of the structural integrity of tissues, transport of molecules and cells, cell migration, cell function and differentiation, and fluid retention and regulation. The clinical benefits of HA in the horse are well published.

Hyaluronic acid is one of many glycosaminoglycans of physiological significance. Other are Chondroitin sulfate, Heparin sulfate, and Dermatan sulfate. The HA molecule is very similar to that of Chondroitin sulfate. In numerous studies, the oral absorption of CS, HS, and DS have been well documented. The bioavailabilities range from 15-20%. Hyaluronic acid has been shown to be absorbed through skin and reach the dermal lymphatics. Also, high levels of hyaluronan has been detected in the intestinal lymphatics. In addition, studies have been performed to determine the effects of HA secreted in saliva. Others have looked at hyaluronic acid production by oral epithelial cells. There is a beneficial effect when Glucosamine sulfate, Chondroitin sulfate, and Hyaluronic acid are administered orally. Generally, the oral

administration of embodiments of the present composition has a quicker clinical response than is produced when each component of the composition is given individually. A significant difference is an acute or a rapid relief in joint pain inflammation and swelling achieved by oral administration of the composition. A dramatic improvement over seven to ten days is achieved whereas it usually takes weeks for that effect to occur. Another benefit received is that of oral preparation and administration of HA given, for example, in the equine in any formulation. The administration of the HA composition orally and having a clinical effect eliminates more evasive procedures. Other ways to give HA would be more invasive, such as injection by IV or other administration into the joints. Basically, embodiments of the present invention may include an oral preparation that is less evasive and also may include an embodiment which is the only oral way to give HA. This provides another alternative to giving it by an injection.

Another benefit is that embodiments of the present invention, with it's high dose of Glucosamine sulfate, Hyaluronic acid, and Chondroitin sulfate, appears to have a synergistic effect which hastens the clinical response.

One embodiment of the present invention is a unique formulation that combines

Glucosamine sulfate, Chondroitin sulfate, and Hyaluronic acid into a paste formulation for direct

oral administration or top dressing feed. This is the only product available which combines these
three substances which are critical for cartilage metabolism and production of synovial fluid.

Also, this embodiment is the only oral paste formulation available for any one of these
supplements. Early clinical trials have shown that when the three products are combined, they

have a synergistic effect. The clinical effects have been impressive. Data has shown a quicker clinical response when GS, CS, and HA are combined than when they are used individually. Conditions in which embodiments of the present invention would be beneficial:

- 1) Osteoarthritis
- Joint effusion
- 3) Joint inflammation and pain
- 4) Post operative arthroscopic surgery
- 5) Restoring proper joint function
- Promote metabolic activity of chondrocytes (cartilage producing cells)
- 7) Inhibit enzymes that degrade cartilage
- 8) Stimulate the production of Hyaluronic acid

Embodiments of the present invention possess the following adayantages:

- 1) Only paste formulation on market
- 2) Only combination of GS, CS, HA in a paste formulation
- 3) Only oral paste form of Glucosamine
- 4) Only oral paste form of Chondroitin
- 5) Only oral paste form of Hyaluronic acid
- Only oral paste in a molasses flavored base

One embodiment of the present invention possesses a molasses flavor. Other flavors would include apple, cherry, and any other palatable flavor.

One embodiment of the present invention comprises the following:

| | W 17/0 |
|---------------------|--------|
| Glucosamine sulfate | 46.03 |
| Chondroitin sulfate | 4.60 |
| Sodium Hyaluronate | 0.18 |
| Manganese sulfate | 0.18 |
| Powdered sugar | 8.70 |
| Xanthan gum | 0.10 |
| Molasses | 25.00 |
| Water | 14.00 |
| Glycerine | 0.70 |
| Corn Starch | 0.30 |
| Sodium Benzoate | 0.50 |
| | |

Embodiments of the present invention in a paste formulation has many advantages. When adding to feed, the formulation will stick to grain to insure total consumption. Embodiments of the paste formulation can be given orally (direct administration) or added to feed--depending on management of animals (turned out in field vs stall confinement). Other advantages include the following:

- 1) Better absorption with liquids
- 2) Molasses flavored paste--more palatable
- 3) Sticky consistency--animal cannot spit product from mouth which insures total dose
- 4) Syringe dose insures more accurate dose

5) Brown sugar included--more paltable

Effects of GS vs CS:

Glucosamine sulfate:

- 1)Enhances chondrocyte synthesis
- 2)Enhances synthesis of hyaluronic acid
- 3)Reduces joint pain
- 4)Reduces synovitis
- Chondroitin sulfate:
- 1)Also helps with chondrocyte synthesis
- 2)CS has been found to inhibit degradative enzymes in cartilage
- 3)CS strengthens and enhances vessels that feed joints or supply them with nutrients by reducing arterial plaque and clear cholesterol deposits
- 4)Reduces joint pain and improves joint mobility
- 5)Reduces synovitis associated with joint arthritis

Neither GS or CS fulfills the quest for the ideal chondroprotective/restorative agent separately but when combined they appear to provide the necessary components for the health and wellbeing of the joint. Hyaluronic acid complements the combination by helping to restore the HA levels needed for joint health and lubrication which are decreased when synovitis is present.

Hyaluronic acid was discovered in 1934 by Meyer and Palmer. It is an important component of the intercellular matrix. HA is ubiquitous in the organism, with the highest level

in soft connective tissue. Specifically, the highest levels are found in the eye and synovial fluid of joints. In joints, its primary role is that of lubrication, reducing pain, and inflammation. In arthritic joints HA is deficient.

Hyaluronic acid is a glycosaminoglcan. Other glycosaminoglycans are Chondroitin sulfate, Heparin sulfate, and Dermatan sulfate. The most abundant GAG is Chondroitin sulfate. The three related GAGs have been found to be absorbed orally. Because of their chemical similarities and the clinical reports of improvement of synovitis, HA has a synergistic effect with GS and CS when given orally. This effect is observed as a more rapid clinical response than when GS and CS are given individually.

Clinically, responses are seen in 7 to 10 days vs three to four weeks or not at all when GS and CS are given without HA. Therefore, we have seen a dramatic decrease in synovitis when HA is combined with GS and CS. This leads us to conclude that HA is absorbed orally and effective either alone or in combination with GS and CS. Therefore, an additional embodiment of the invention comprises a composition including HA and any acceptable carrier, such as the paste formulation disclosed herein and any other liquid, powder, gel or similar type carrier.

Another embodiment of the invention includes a paste formulation containing the active component isoxuprine. Isoxuprine is a vasodilator and is utilized in treatment of many afflictions including the treatment of navicular disease. One effect of isoxuprine is that it stimulates the vasodilator nerves, such as the vaso-inhibitory and vasohypotonic nerves, and causes dilation or relaxation of the blood vessels. Administration of isoxuprine to a patient, such as an animal, in the form of a paste is beneficial to ensure adequate administration.

While the invention has been described in conjunction with specific embodiments thereof, it is evident that many alternatives, modifications, and variations will be apparent to those skilled in the art in light of the foregoing description. Accordingly, it is intended to embrace all such alternatives, modifications, and variations which fall within the spirit and broad scope of the invention.

LOT 101013 CHONDROGEN EQ PROCEDURE BATCH SIZE:068.559 KG BULK DENSITY: 11.75LBS/GAL

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| 100 | 14.4 | 23.5 | 0.2 | 0.7 | 0.2 | 0.7 | 20 | 0.144 | 0.144 | 4 | 36 | WT% | | | |
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BALL MILLING OPERATION FOR POWDERED PREMIX LOT NO TOIDIS

PART 1 OF 5

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PART 2 OF 5

BALL MILLING OPERATION FOR POWDERED PREMIX

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PART 3 OF 5

BALL MILLING OPERATION FOR POWDERED PREMIX

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PART 4 OF 5

BALL MILLING OPERATION FOR POWDERED PREMIX

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PART 5 OF 5

BALL MILLING OPERATION FOR POWDERED PREMIX

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| LABEL POWDERED PREMIX EQ | PACKAGE INTO NEW 55 GAL OPEN HEAD POLY WITH POLY LINER | TURN ON BALL MILL AND ALLOW TO MIX FOR 24 HOURS | HAVE SUPERVISOR OR ANOTHER OPERATOR VERIFY WEIGHT INITIALS OF CHECK | WEIGH OUT 22.5 KGS (49.5 LBS) OF SUGAR INTO A CLEAN PAIL | CODE NUMBER MATCHES WITH 1255 HAVE SUPERVISOR VERIFY PRODUCT AND LOT NO 86. 602.05 - 10.07 (SUPVRS INT | CHECK CODE NUMBER AND WRITE IT DOWN HERE 1255 | RECEIVE SUGAR POWDERED CANE 10-X | CHARGE CHONDROITIN INTO THE BALL MILL CLOSE UP ANY PARTIAL DRUMS AND LIST PIECE WEIGHT 42.8 | HAVE SUPERVISOR OR ANOTHER OPERATOR VERIFY WEIGHT INITIALS OF CHECK | WEIGH OUT 4.48 KGS (9.88 LBS) INTO A CLEAN NEW PAIL | CODE NUMBER MATCHES WITH 7844 | CHECK CODE NUMBER AND WRITE IT DOWN HERE 7899 | RECEIVE DRUM OF CHONDROITIN SULFATE 90% | CLOSE UP ANY PARTIAL DRUMS AND LIST PIECE WEIGHT21. | HAVE SUPERVISOR OR ANOTHER OPERATOR VERIFY WEIGHT | HAVE SUPERVISOR VERIFY PRODUCT AND LOT NO 2005 3 SUPVRS INT 1 | CHECA COUR NOWBERT AND WINTER 1 DOWN THE COURT OF THE COU | THECEIVE 2@25KGS DRUMS OF GLUCOSAMINE SULFATE. | |

| | 190 | Ge o | 100 | | | | | |
|----------------------------|----------------|--|--|---|---|--|-------------------------------|--|
| | 96 | SW. | dir | • | | | | |
| EMPT IT RENOTOR AND WEIGHT | MIX FOR 1 HOUR | ADD THE XANTHANGLOERINE/WATER MIXTURE TO REACTOR | ADD 1.33 KGS OF CITRIC ACID ANHYDROUS TO THE BATCH REACTOR | HAVE SUPERVISOR OR ANOTHER OPERATOR VERIFY WEIGHT | WEIGH OUT 1.33 KGS (2.94 LBS) OF CITRIC ACID ANHYROUS | HAVE THE SUPERVISOR VERIFY PRODUCT AND LOT NUMBER SUPVRS INT | CODE NUMBER MATCHES WITH 9114 | CHECK CODE NUMBER AND WRITE IT DOWN HERE 9 114 |

XANTHAN GUM PREPARATION

| | l. l. | k I. : | DATE I | XANTHAN GUM PREPARATION |
|-----------------------------|--|---|--|-------------------------|
| | 1800 | 130 | TIME 13 % | STATE |
| | 20 2 | £ 5. | OPER M/S | KCA I JON |
| MIX FOR 2-3 HOURS OR LONGER | HAVE THE SUPERVISOR VERIEY PRODUCT AND LOT NUMBER SUPVRS INT 1 WEIGH OUT 1.33 KGS (2.93 LBS) OF XANTHAN GLM A CHARGE MATERAL SLOWLY INTO BLENDER AND MIX WHEN CONSISTANT MIXTURE -DILUTE BY ADDING 11.6 LBS OF DI WATER TO MIXTURE | HAVE SUPERVISOR VERBITY PRODUCT AND LOT NUMBER(\$\to 9.07.26\times). SUPVRS INT \(\) WEIGH OUT 4.86 KGS (10.28 LBS) OF GYLCERINE CHARGE MATERIAL INTO BLENDER RECEIVE THE XANTHAN GUM CHECK THE CODE NUMBER AND WRITE IT DOWN HERE \(\frac{9.34}{5} \) CHECK THE CODE NUMBER AND WRITE IT DOWN HERE \(\frac{9.34}{5} \) CODE NUMBER AND WRITE IT DOWN HERE \(\frac{9.34}{5} \) | RECEIVE GYLCERINE CHECK THE CODE NUMBER AND WRITE IT DOWN HERE. 9.34 7 CODE NUMBER MATCHES WITH 9347 | |

LIQUID/ SALTS MIXTURE PRPARATION LOT NO

| | 15/1 | TIME SECTION |
|-------|------|-----------------|
| 36 35 | 1 1 | 38 |
| 135 | ŧ | Ò |
| | M | 130 |

R 10

13,50 36 CHARGE SLOWLY BY SPRINKLING IN OVER 1 HR SPAN HAVE SUPERVISOR OR ANOTHER OPERATOR VERIFY WEIGHT WEIGH OUT 951GRAMS OF SODIUM HYALURONATE HAVE SUPERVISOR VERIFY PRODUCT AND LOT NO COSTE CHECK CODE NUMBER AND WRITE IT DOWN HERE 6409 RECEIVE MAGANESE SULFATE AGITATE CODE NUMBER MATCHES WITH 6909 SUPVRS INT INITIALS OF CHECK

240 ADD 952 GRAMS OF MANGANESE SULFATE TO THE BATCH REACTOR HAVE SUPERVISOR OR ANOTHER OPERATOR VERIFY WEIGHT HAVE SUPERVISOR VERIFY PRODUCT AND LOT NO. õ SUPVRS INT

30 11 3 RECEIVE THE SODIUM BENZOATE MIX FOR 15 MINUTES

WEIGH OUT 4.67 KGS (10.29 LBS) OF SODIUM BENZOATE HAVE SUPERVISOR VERIFY PRODUCT AND LOT NUMBER AND LOT NUMBER CODE NUMBER MATCHES WITH 9517 CHECK CODE NUMBER AND WRITE IT DOWN HERE 9517 HAVE SUPERVISOR OR ANOTHER OPERATOR VERIFY WEIGHT INITIALS OF CHECK SUPVRS INT

200 RECEIVE THE CITRIC ACID ANHYDROUS MIX FOR 15 MINUTES

ADD 4.67 KGS OF SODIUM BENZOATE TO THE BATCH REACTOR

30

LOT NO I SICIOIS

LIQUID PREMIX FOR EQ

PART 2 OF 2

DATE 80. TIME 30 HAVE SUPERVISOR VERIFY PRODUCT AND LOT NO LOCK 7/1 SUPRVSR INT CODE NUMBER MATCHES WITH 1147 CHECK CODE NUMBER AND WRITE IT DOWN HERE 1/47 RECEIVE MOLASSES IN BATCH REACTOR PREPARE FOR FINAL BLENDING OF LIQUID COMPONENTS

57 H. DISCHARGE INTO NEW POLY DRUMS MIX FOR 4 HOURS CHARGE LIQUID SALTS PREMIX TO REACTOR TURN ON AGITATOR

CHARGE 156.67KGS (345.4 LBS) OF MOLASSES INTO REACTOR

1300

200 LABEL LIQUID PREMIX EQ

LOT NO TOICES

DISPERSING POWDER AND LIQUID PREMIX TOGETHER

DATE 312 1800 TIME IN A BATCH DISPERSER, SET UP FOR CHONDROGEN EQ ADJUST FOR SOLID FEED ADJUST FOR LIQUID FEED BLEND MATERIALS AND PACKAGE START WEIGHT OF FINAL PRODUCT 1340 FINISH

PACKAGING FROM DRUMS TO PAILS

TIME OPER RE

PATE 9/18

RECEIVE APPROVED MATERIAL CHONDROGEN EQ VERIFY LOT NO

PACKAGE INTO 5 GAL CLEAN OPEN HEAD POLY PAILS AT 50 LBS NET

LOT NO TOIDIS

SAMPLE RECEIVED

TEST FOR PH (5%) 4. TEST FOR VISCOSITY 18, pc?

ACTUAL LOT ANALYSIS: SPECIFICATION NO. 4917-13-EL

SODIUM HYALURONATE, Powder

| Description: | Fine white | powder, with no odor | |
|--------------|--|--|--|
| Actual Lot A | nalysis: | Specification | Actual |
| a) Estee La | uder Requirements: Infrared Spectrum pH of a 0.5% acqueous solution Water Content [KF] Residue On Ignition Protein Content Uronic Acid Content (dry basis) Sodium Hyaluronate (dry basis) Total Aerobic Plate Count Non-Conkoming Organisms | To Pass Test 6 - 8 5 10% 7 - 10% 50.1% 45.0-48.4% 93-100% 51000 CPU/g None Recovered | Passes 7.3 5.8% 7.6% <0.1% 47.8% 98.8% Passes Passes |
| b) Other | Parameters Solubility © 0.5% W/V in freshi Appearance of a 0.5% aqueous (clear-sightly opalescentalar) Total Nitrogen (dry basis) Sodium Glucuronate (dry basis) Molecular Weight Preservative | s solution less viscous liquid) To Pass Test 3.0 - 3.6% | Passes 3.4% 53.2% 1.65x10° None |
| el . If 1 *F | | | |

Shelf Life: 2 years

Packing: 500 g poly containers with tamper-proof safety seals

Lot Size: 10 kg

Approval:

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K

We believe the information havin to be reliable, framers, no versory, express or mybed, or made as to its according or complemess and none is made to its these of the inequalities entry property. 12 CODP shall not be both

CERTIFICATE OF ANALYSIS

Commodity: D-Glucosamine Sulfate.2KCL Date of Analysis: 5/23/00

Batch No.: 20000503

| | Guaranteed Specification | Test Result | |
|-----------------------|---------------------------------|--|---------|
| Appearance: | White Crystallinc Powder | Conforms | |
| Assay: | 98% - 101% | 99,2% | |
| -[α] ²⁶ b: | +49" - +55° | 149.90 | |
| Loss on drying: | ≤0.5% | 0.38% | |
| Residue on ignition: | 26.5% - 29.8% | 28.2% | |
| (ron (Fe): | <10ppm | <10ppm (3) | |
| Heavy Metals: | ≤l0ppm | <10ppm | Phone & |
| Arsenic: | ≤0.5ppm | <0.5ppm | 4 |
| pH Value: | 3.0 - 5.0 | 4.5 | \$ |
| Chloride: | 11.2% - 12.3% | 12.0% | 8 |
| Bulk Density: | 20.85g/cc | 0.89g/cc # C | 3 |
| Total Plate Count: | <5000cfu/g | 487c/w/g | 12 |
| Yeust & Mold: | <100cfu/g | 0.89ycc ago 2487cfu/g 37cfu/g Ncestive | Deg. |
| E. Coli: | Negative | Negative de la | 3 € |
| Salmonella: | Negative | Negativo | |
| Packing: | 25kg net each fiber drum with d | ouble PE lincr. | |
| Quantity; | 1,000kg = 40 x 25kg drums | | |

Certificate of Analysis

Product Name:

Chondroltin Sulfate 90% Min.

Batch No.:

HS000530

| Assay: | 90% Min. | 91.7% |
|------------------|---------------|-----------|
| Loss on Drying: | 10% Max. | 8.6% |
| PH: | 5.5 - 7.5 | |
| Bulk Density: | 0.6 g/ml Min. | 0,88 g/ml |
| Nitrogen: | 2.5% - 3.8% | 3.1% |
| Heavy Metal: | 10 ppm Max. | 9.4 pm |
| Chloride: | 1% Max. | Pass |
| Other Bacterium: | 300/g Max. | Pass |
| Mold: | 100/g Max. | Pass |
| Clear Degree: | Transparent | Pass |

NOTE THE ABOVE INFORMATION IS BASED ON THE CERTIFICATE OF ANALYSIS RECEIVED FROM OUR SUPPLIER AND IS NOT INTENDED AS A SUBSTITUTE FOR STRICT QUALITY CONTROL ANALYSIS BY THE PURCHASER OF THIS PRODUCT

| | | A K | TERIAL SA | FETY O | ATA SHE | t I | | |
|------------------|--------------------------------|-----------------|-------------------|--------------|---------------|-------------|------------------|--|
| T: CHONOROGEN EQ | | | | | | | | |
| | SECTION 1: GENERAL INFORMATION | | | | | | | |
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| A HAIS HAZARO RA | TINE | | | | MFPA 784 DERI | IVED HAZARÎ | RATING | |
| t: | 8 | LEAST | | KE | EALTH; | • | LEAST | |
| | ŧ | LEAST | | F1 | RE: | • | LEAST | |
| IVIIY: | 9 | LEAST | | 8.6 | ACITVITY: | | LEAST | |
| (ALPROTECTION: | X | ASK SUPERVISOR | | 01 | IKER: . | 1 | L ASK SUPERVISOR | |
| | | | | | | | ********** | |
| | | | SECTION 2: H | AZAROGUS IN | REDIENIS | | | |
| io W | | | O CLASSIFICATION: | CORRZARION | 82 | | | |
| | | | CASE | | RAZARO | | LIMITS | |
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| DINTE CURRENTLY | | | | | | | | |
| 9 1918.1288. | | | | | | | | |
| 0 | | | | | | | | |
| | | | | 3: PHYSICAL | DATA | | | |
| ********** | | | *********** | | | ~~~~ | ************ | |
| | 8.A | , 11 1 | | | | | | |
| ILITY IN WATER: | SOL | UBLE | | | | | | |
| FIC GRAVITY: | N.0 | | | | | | | |
| RANCE: | OPS | QUE BROWN PASTE | | | | | | |

NO = NOT DETERMINED NA = NOT APPLICABLE

WATERTAL SAFETY BATA SH

| T: CHONOROGEN EQ | KSDS NO: 48-581A |
|------------------------------|--|
| | SECTION 4: FIRE AND EXPLOSION DATA |
| ~~~~~~~~~~ | |
| POINT: | N.A. |
| UISHING METHOD: | USE WATER, CARBON DISKIDE, DRY CHENICAL OR FORM. |
| : FTOE FTENTING PROFFAURFS. | USE SELF CONTAINED BREATHING APPARATUS. |
| C 11sc 11du11sd capacabaca. | |
| L FIRE FIGHTING PROCEDURES: | NORE KNOWK. |
| | |
| | SECTION 5: REACTIVITY DATA |
| | *************************************** |
| ITY | 318472 |
| OUS POLYMERIZATION: | MIET HOL ECCOR |
| DSITION PRODUCTS: | HOT ESTABLISHED. |
| IONS AND MATERIALS TO AVOID: | HORE KNOWN. |
| (I) | 1 |
| | SECTION 6: MEALTH HAZARO DATA |
| Ü | SECTION 6: HEALIN MACAND DATA |
| V. | |
| OMEXPOSURE: | EYES YES SKIN YES INGESTION YES INHALATION YES |
| W | |
| in a | SYMPTOMS OR ACUTE MEALTH HAZARDS |
| ti h. i | WAY CAUSE EYE IRRITATION. |
| Cest | |
| (Aug | NO EFFECTS EXPECTED UNDER NORMAL BSE. |
| 2.1 | WOT ESTABLISHED. |
| (A) | |
| ATION: | NO EFFECTS EXPECTED UNGER NORMAL USE. |
| | 33.4 |
| IC HEALTH HAZARDS: | BEHZIJEATZE TOM |
| HORENICITY: | NTP ARC BSHA |
| | FIRST AID |
| | FIUSH EYES WITH WATER FOR AT LEAST 15 MIRUTES. |
| | IF IRRITATION OCCURS, GET MEDICAL ATTENTION. |
| | WASH EXPOSED AREAS WITH SOAP AND WATER. IF IRRITATION |
| | PERSIST, SEEK MEDICAL ATTENTION. |
| FION: | INDUCE VONITING BY GIVING 2 GLASSES OF WATER AND PLACE |
| | FINGER BOWN THROAT. CALL A PHYSICIAN. HEVER GIVE |
| | ANYTHING BY MOUTH TO AN UNCONSCIOUS PERSON. |
| TIOK: | IF AFFECTED, REMOVE INDIVIDUAL TO FRESH HIM. |
| TIOK: | FLUSS ETES MITH WATER FOR AT LEAST IS MINUTES. IT TREITATION OCCURS, OR FRACICAL ATTENTION. WASH EXPOSED AREAS WITH SOAP AND MATER. IF IRRITATION PERSIST, SEER REDICAL ATTENTION. INDUCT VOMETINE BY GIVINE 2 GLASSES OF MATER AND PLACE FIRMER BOUNT MERGAT. CALL A PRISTCHAR. MEVER GIVE ANYTHING BY MOUTH OF AN MEMORSCHOUS PERSON. IF AFFECTED, REMOVE INDIVIDUAL TO FRESH AIR. |

NATERIAL SAFETY BATA SHEET

| T: CHONOROGEN EQ | #SOS #0: 88-581# |
|----------------------|---|
| | SECTION 7: PRECAUTIONS FOR SAFE HANDLING AND STORAGE |
| 0I If 88 SP | NTILATE AREA, PERSONS PERFORMINE CLEAR-UP SHOULD WEAR ADEQUATE PROTECTION COUTPAENT. CONTAIN MATERIAL BY CING THE AREA AROUND THE SPILL. IF THE PRODUCT IS AN A SOLID FORM, SHOWEL EXECUTY WHO RECOVERY OBUNS. THE PRODUCT IS A LIQUID, IT SHOULD BE PICKED UP USING A SOLIDADLE ASSEMBANT MATERIAL, THEN SHOWLED TO OCCURY DAWNS. IT THE ARTERIAL IS RELEASED INTO THE ENVIRONMENT, THE USES MUDIC DETERMINE WHETHER THE LLL SHOULD BE REPORTED TO THE APPROPAINTE LOCAL, STATE, AND FEDERAL ANTHORITIES. ISSUIT ILCAL, STATE, AND FEDERAL RECULATIONS EREFORE OF TIES ARTERIAL. SELLY LOCAL, STATE, AND FEDERAL RECULATIONS EREFORE OF TIES ARTERIAL. |
| | SECTION 8: PROTECTIVE EQUIPMENT |
| | WANE WOODSIAY WEERER |
| | NOME MORRALLY MEDDO. NO SPECIAL REDUIRERENTS. COUVES FACESHIELD APRON GOGGLES YES INPERVIOUS COVERALLS |
| NYSIENIC PRACTICES: | AS WITH ALL INDUSTRIAL CHEMICALS, CARE SHOULD BE TAKEN TO AVOID COSTACT WITH EYES, SIIN, AND CLOTHING. HAMOS AND UMPROTECTED SIN SHOULD BE THOROUGHLY MASHED AND COMTACINATED CLOTHING SHOULD BE CANNEED PRIOR TO ANY DISECT PRESONAL CONTACT, ALL EMPOSED CLOTHING SHOULD BE LAUNDERED PER HORNAL CARE INSTRUCTIONS DEFORE REUSE. |
| 199 | SECTION S: REGULATORY DATA |
| IELISARA: | THE FOLLOWING DATA IS BIIND SUPPLIED IN COMPLIANCE WITH TITLE III SUPERFUND ANEADMENTS AND REMUTHORIZATION ACT (SARA) PART 313 AND 40 CFM 372: |
| a u | TRIS PRODUCT DOES NOT CONTAIN ANY CHEMICALS FOUND ON THE SARA LIST IN 40 CFR 372. |
| PORTATION: | NOT RESULATED BY D.O.T. |
| O | S: CONTAINS NO MATERIALS KNOWN TO BE ON THE CALIFORNIA PROPOSITION 68 LIST |
| | SECTION 18: TOXICOLOGY |
| | HO DATA AVAILABLE FOR CHRONIC OVERENPOSURE. |
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| | DISCUINER |
| T. THE INFORMATION | REIN IS BELIEVED TO BE ACCURATE BUT IS NOT WARRENTED TO BE WHETRER ORBINATING WITH TRIS COMPANY IS OFFERED SOLELY FOR TOUR CONSIDERATION. RECIPIENTS ARE ADVISED TO CONFIRM IN ADVANCE ITION IS CURRENT, AND SUITABLE FOR THEIR NEEDS. |
| | NO = NOT DETERMINED — NA = NOT APPLICABLE |

MATERIAL SAFETY DATA SHEET

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| : PUS PRENIX EQ | | | | | MCDC NO. 6 | 44.1214 | | |
| | | | SECTION 1: 6 | FRERAL TREAS | MATTON | | | |
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| | | | I STEE | MERA RATIN | | | | |
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| HNIS HAZARO RA | TING | | | | MFPA 784 DERI | EVED HAZAR | RATING | |
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| | 8 | LEAST | | FI | te: | 8 | TEAST | |
| ITY: | 9 | LEAST | | RE | CITVITY: | 8 | LEAST | |
| 1914 | | ASK SUPERVISOR | | | IER: • | | ASK SUPERVISOR | |
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| to other | **** | | | | | | | |
| M | | HAZARD | CLASSIFICATION: 1 | IONHAZARDOUS | | | | |
| PTHETTEGORY | | | CASE | | HAZARD | | LIMITS | |
| ENTS CURRENTLY | HOT | | | | | | | |
| U⊊™H ACCORDANC 1933.1200. | ų 2. | | | | | | | |
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| | | | SECTION 3 | : PHYSICAL | JATA | | | |
| | N.A. | . N \$ | | | | | | |
| ITY IN WATER: | | | | | | | | |
| C GRAVITY: | | | | | | | | |
| | | UF RROWN PASTE | | | | | | |
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NO = NOT DETERMINED NA = NOT APPLICABLE

NATERIAL SAFETY DATA SHEET SECTION 4: FIRE AND EXPLOSION DATA H.A. POINT: JISHING METHOD: USE WATER, CARBON DIDXIDE, DRY CHEMICAL OR FORM. : FIRE FIGHTING PROCEDURES: USE SELF CONTAINED BREATHING APPARATUS. : FIRE FIGHTING PROCEDURES: MORE KNOWN. SECTION 5: REACTIVITY DATA STABLE TIY WILL NOT OCCUR OUS POLYMERIZATION: OSITION PRODUCTS: NOT ESTABLISHED. IONS AND MATERIALS TO AVOID: HOME KNOWN. SECTION 6: HEALTH HAZARD DATA 1/4/ EYES YES SKIN YES INGESTION YES INHALATION YES ORIEXPOSURE: 31 SYMPTOMS OR ACUTE HEALTH HAZARDS 00 MAY CAUSE EYE IRRITATION. HO EFFECTS EXPECTED UNDER HORMAL USE. NOT ESTABLISHED. NO EFFECTS EXPECTED UNDER NORMAL USE. NOT ESTABLISHED C MEALTH HAZARDS: MTP ARC 4888 OGENICITY: FIRST AID FLUSH EYES WITH WATER FOR AT LEAST 15 MINUTES. IF IRRITATION OCCURS, GET MEDICAL ATTENTION, WASH EXPOSED AREAS WITH SOAP AND WATER. IF IRRITATION PERSIST, SEEK MEDICAL ATTENTION. INDUCE VONITING BY GIVING 2 GLASSES OF WATER AND PLACE 18%: FINGER DOWN THROAT. CALL A PHYSICIAN. HEVER SIVE

ANYTHING BY MOUTH TO AN UNCONSCIOUS PERSON. IF AFFECTED, REMOVE INDIVIDUAL TO FRESH AIR.

TERM:

NO - NOT DETERMINED NA - NOT APPLICABLE

MS0S NO: 89-191A

SECTION 7: PRECAUTIONS FOR SAFE NAMBLING AND STORAGE

VENTILATE AREA, PERSONS PERFORMING CLEAN-UP SHOULD WEAR ADEQUATE PROTECTION EQUIPMENT. CONTAIN MATERIAL BY DIKING THE AREA AROUND THE SPILL. IF THE PRODUCT IS IN A SOLID FORM, SHOVEL DIRECTLY INTO RECOVERY DRUKS. IF THE PRODUCT IS A LIQUID. IT SHOULD BE PICKED UP USING A SUITABLE ABSORDANT NATERIAL, THEN SHOVELED TO RECOVERY DRUMS. IF THE MATERIAL IS RELEASED INTO THE ENVIRONMENT, THE USER SHOULD DETERMINE WHETHER THE

DISPOSAL METHOD: CONSULT LOCAL, STATE, AND FEDERAL REGULATIONS BEFORE OF THIS MATERIAL.

SPILL SHOULD BE REPORTED TO THE APPROPRIATE LOCAL, STATE, AND FEBERAL AUTHORITIES. HE AND STORAGE: MATERIAL SHOULD BE STORED IN ITS OWN CONTAINER AND SHOULD ALWAYS BE KEPT COVERED WHEN HET IN USE SECTION 8: PROTECTIVE EQUIPMENT ATORY PROTECTION: MORE HORMALLY MEEDED. NO SPECIAL REDUIREMENTS. TIVE EQUIPMENT: GLOVES ___ FACESHIELD ___ APRON ___ GOGGLES YES IMPERVIOUS COVERALLS VOIENIC PRACTICES: AS WITH ALL INDUSTRIAL CHERICARS, CARE SHOULD BE TAKEN TO AVOID CONTACT WITH EYES, SXIM. AND CLOTHING. HANOS AND UNPROTECTED SKIN SHOULD BE THOROUGHLY WASHED AND CONTANTHATED CLOTHING SHOULD BE CHANGED PRIOR TO ANY DIRECT PERSONAL CONTACT. ALL EXPOSED CLOTHING SHOULD BE LAUNDERED PER HORMAL CARE INSTRUCTIONS REFORE REUSE. SECTION 9: REGULATORY DATA-THE FOLLOWING DATA IS BEING SUPPLIED IN COMPLIANCE WITH TITLE III SUPERFUND ANENDMENTS AND III SARA: REAUTHORIZATION ACT (SARA) PART 313 AND 48 CFR 372: ti. W. THIS PRODUCT DOES NOT CONTAIN ANY CHEMICALS FOUND ON THE SARA LIST m IN 48 CF8 372. 41 155 NOT REGULATED BY D.O.T. SRTATION: ځو 12 AND THE CALIFORNIA PROPOSITION 65: CONTAINS NO MATERIALS KNOWN TO BE ON THE CALIFORNIA PROPOSITION 65 LIST NO DATA AVAILABLE FOR CHRONIC OVEREXPOSURE.

FORMATION GIVEN HEREIN IS BELIEVED TO BE ACCORATE BUT IS NOT WARRENTED TO BE WHETHER ORGINATING WITH THIS COMPANY . THE INFORMATION IS OFFERED SOLELY FOR YOUR CONSIDERATION. RECIPIENTS ARE ADVISED TO CONFIRM IN ADVANCE

TO THAT THE INFORMATION IS CURRENT, AND SUITABLE FOR THEIR MEEDS.

NO = NOT DETERMINED NA = NOT APPLICABLE

MATERIAL SAFFTY BATA SHE

| : LIQ PREMIX EQ | | | | #585 MO: 4 | 18-197A | | | |
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| SECTION 1: GENERAL INFORMATION | | | | | | | | |
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| HMIS HAZARO RA | TINS | | | MFPA 706 DERI | IVED HAZARO RATING | | | |
| | 8 | LEAST | | HEALTH: | 8 LEAST | | | |
| | | LEAST | | FIRE: | # LEAST | | | |
| | | LEAST | | REACITVITY: | 8 LEAST | | | |
| PROTECTION: | X | ASK SUPERVISOR | | OTHER: · | I ASI SUPERVISOR | | | |
| W | | | SECTION 2: HAZARDOUS | INSREDIENTS | | | | |
| (2) | | | CLASSIFICATION: NORHAZA | | | | | |
| ul Ti | | DALAGE | | | LIMITS | | | |
| US INGREDIENTS | | | CAST | MAZARO | (1811) | | | |
| ENTS CURRENTLY USEIN ACCORDANC | KOT | | | | | | | |
| 1949.1200. | 10 | | | | | | | |
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| | | | SECTION 1. PHYSI | CAL BATA | | | | |
| | 8.4. | | | | | | | |
| | | | | | | | | |
| .ITY IN WATER: | | | | | | | | |
| C GRAVITY: | N,0. | | | | • | | | |
| NCE: | 6940 | GE BROWN PASTE | | | | | | |
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) = NOT BETERMINED NA = NOT APPLICABLE

NATERIAL SAFETY BATA SHEET MINT: HISHING METHOD: USE WATER, CARBON DIOXIDE, DRY CHEMICAL OR FOAM. . FIRE FIGHTING PROCEDURES: USE SELF CONTAINED BREATHING APPARATUS. . FIRE FIGHTING PROCEBURES: NONE KNOWN. SECTION 5: REACTIVITY DATA STABLE WILL NOT OCCUR DUS POLYMERIZATION: SSITION PRODUCTS: HOT ESTABLISHED. TORS AND MATERIALS TO AVOID: NONE KNOWN. EYES YES SKIN YES INGESTION YES INHALATION YES ORYEXPOSURE: 155 SYMPTOMS OR ACUTE HEALTH HAZARDS MAY CAUSE EYE IRRITATION. NO EFFECTS EXPECTED UNDER MORNAL USE. NOT ESTABLISHED. NO EFFECTS EXPECTED UNDER NORMAL USE. NOT ESTABLISHED E HEALTH BAZAROS: ARE 888A MIP OGENICITY: FIRST AID FLUSH EYES WITH WATER FOR AT LEAST 15 MINUTES. IF IRRITATION OCCURS, GET MEDICAL ATTENTION. WASH EXPOSED AREAS WITH SHAP AND WATER. IF IRRITATION

WASH EXPOSED AREAS WITH SUMP AND MATER. IF IRRITATION PRESST, SEEN HOUSEAL ATTENTION.
INDUCE VONITHE BY SIVING 2 BLASSES OF MATER AND PLACE FIMER BOWN THROAT. CALL A PHYSICIAN. HEVER SIVE ANTIBLES BY WOUTH TO AN WEORSCHOUS PRESS AT N.
IF AFFECTED, REMOVE INDIVIOUAL TO FRESH ATR.

TON:

.TION:

NO = NOT DETERMINED - NA = NOT APPLICABLE

| : LIQ PRENIX EQ | NSBS NG: 84-182A |
|------------------|---|
| | SECTION 7: PRECAUTIONS FOR SAFE RANDLING AND STORAGE |
| TORREST METHOR. | VENTILATE AREA, PERSONS PERFORATING CLEAN-UP SNOULD WEAR ADCOUNTE PROTECTION EQUIPAENT. CONTAIN MATERIAL BY DIETHS THE AREA AROUND THE SPILL. IF THE PRODUCT IS IN A SQUIJA FORM, SHOWED DIRECTUR THTO RECOVERY DRUMS. IF THE PRODUCT IS A CLUDIO, IT SHOULD BE PICKED UP USING A SULTABLE ASSORBANT ANTECHALT, WHEN SHOVELED THE RECEVERY DRUMS. IF THE MATERIAL IS RECEASED INTO THE EMPLOAMENT, WHE USER SHOULD DETERMINE WHETHER THE SPILL SHOULD BE REPORTED TO THE APPROPRIATE LOCAL, STATE, AND FEDERAL ANTHORITIES. ORIGINAL THE CONSULT OF THE PROPRIATE OFFICE OF THIS MATERIAL. MATERIAL SHOULD BE STORED IN ITS OWN CONTAINER AND SHOULD ALWAYS BE KEPT COVERED WHEN NOT IN USE |
| | SECTION 8: PROTECTIVE EQUIPMENT |
| TORY PROTECTION: | NOME NORMALLY NEFOED. NO SPECIAL REQUIRERANTS. GLOVES FACESHIELD APRON GOGGLES YES IMPERVIOUS COVERALLS |
| GIERIC PRACTICES | : AS WITH ALL INDUSTRIAL CREBICALS, CARE SHOULD BE TAKEN TO AVOID COMTACT WITH ETES, SKIN, AND CLOTHING. HANDS AND UMPROTECTED SCIN SMOULD BE TEOROUGHLY WASHED AND CONTAKISHED CLOTHINS SHOULD BE CHANGED PRIOR TO ANY DIRECT PERSONAL CONTACT. ALL EXPOSED CLOTHING SHOULD BE LAUNDERED PER NORMAL CARE INSTRUCTIONS BEFORE REBSE. |
| (7) | SECTION 9: REGULATORY DATA . |
| (II)gere: | THE FOLLOWING DATA IS BEING SUPPLIED IN COMPLIANCE WITH TITLE III SUPERFUND AMENDMENTS AND REAUTHORIZATION ACT (SARA) PART 313 AND 40 CFR 372: |
| ii iii iii | THIS PRODUCT DOES NOT CONTAIN ANY CHEMICALS FOUND ON THE SARA LIST IN 48 CFR 372. |
|)RIATION: | NOT RESULATED BY 0.0.T. SS: CONTAINS NO MATERIALS KNOWN TO BE ON THE CALIFORNIA PROPOSITION |
| | 65 LIST |
| | SECTION 10: TOXICOLOGY |
| | NO DATA AVAILABLE FOR CHRONIC OVEREXPOSURE. |
| | |
| ~*** | DISCLATAER |
| THE INFORMATI | MEREIM IS RELIEVED TO DE ACCURATE BUT IS NOT WARRERTED TO RE WHETMER DUBLIRATING WITH THIS COMPANY ON IS OFFERED SOLELY FOR TOUR CONSIDERATION. RECIPIERTS ARE ADVISED TO CONFIRE IN ADVANCE NATION IS CURRENT, AND SUITABLE FOR THEIR NEEDS. |
| | NO = NOT DETERMINED — NA = NOT APPLICABLE |

CLAIMS:

- A Chondroprotective/Restorative composition as disclosed and suggested herein.
- A method of using a Chondroprotective/Restorative composition as disclosed and described herein.
- A Chondroprotective/Restorative composition comprising Glucosamine sulfate (GS), Chondroitin sulfate (CS) and Hyaluronic Acid (HA) and optionally a pharmaceutically acceptable carrier.
- A Chondroprotective/Restorative composition comprising Hyaluronic Acid
 (HA) and optionally a pharmaceutically acceptable carrier.
- A composition comprising Isoxuprine and optionally a pharmaceutically acceptable carrier in an orally administered form.
- The composition of claim 3 and 4 wherein the composition is in an orally administered paste form.
- The composition of claim 3 and 4 wherein the composition is in an orally administered liquid form.
- The composition of claims 3 and 4 wherein the composition is in an orally administered solid form.
- A method of treating or preventing osteoarthritis, joint effusion, joint inflammation and pain, post operative arthroscopic surgery, deterioration of proper joint function, the reduction or inhibition of metabolic activity of

chondrocytes (cartilage producing cells), the activity of enzymes that degrade cartilage, the reduction or inhibition of the production of Hyaluronic acid comprising administering to a species a therapeutically effective amount of a composition including Glucosamine sulfate (GS), Chondroitin sulfate (CS) and Hyaluronic Acid (HA).



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(54) CHONDROPROTECTIVE/RESTORATIVE COMPOSITIONS AND METHODS OF USE THEREOF

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Publication Classification

(57) ABSTRACT

The instant invention provides a method of treating or preventing osteoarthritis, joint effusion, joint inflammation and pain, synovitis, lameness, post operative anthroscopic surgery, deteroristion of proper joint function including joint mobility, the reduction or inhibition of metabolic activity of conjuments and the activity of caryones that degrade cartilage, the reduction or inhibition of the production of Hyaluronic acid, said mothed comprising orally administering to a mammalian species a therapeutically effective amount of Hyaluronic Acid or pharmaceutically acceptable satts thereof. Additionally, compositions containing hyaluronic acid; chondrolius mistlate, and glucosamine sulfate in a paste formulation are also disclosed which can be administered on their own or can be used as a feed additive.

CHONDROPROTECTIVE/RESTORATIVE COMPOSITIONS AND METHODS OF USE THEREOF

FIELD OF INVENTION

[0001] The present invention relates to medically useful preparations based on hydratoric acid and pharmaceutically acceptable salts thereof, a neturally-occurring substance found in animal tissue, and especially in reconstruction, virceous humour, unabilical cords, and synovial fluid or nammals. This invention also relates to new orally administrable formulations containing hydratoric acid. The instant invention is also directed to chondeprotective/restorative compositions containing hydratoric acid. This invention also relates to one up harmaceutical formulations contained hydratoric acid. This invention is further directed to a new veterinary formulations containing hydratoric acid. This invention further relates to orally administrable veterinary formulations containing hydratoric acid.

[0002] The present invention is also directed to veterinary formulations containing hysluronic acid and additional bioeffective active ingredients such as bioactive agents useful in the treatment of domesticated animals especially horses. This invention also provides methods for treating horses in need of chondroprotection. The invention is further directed to pharmaceutical compositions containing byaluronic acid, glucosamine and chondroitin. The present invention also relates to a method of treating aseptic synovitis in horses with hyaluronic acid alone or in combination with other active ingredients. More specifically, the present invention is also intended for therapeutic treatments of arthritis and related conditions using pharmaceutical compositions containing hyaluronic acid as well as other active ingredients effective ion the treatment of joint diseases. The compositions of the invention are particularly useful in the veterinary field but are also very useful in treatment of humans.

[0003] This invention further relates to the oral administration of forms of hydrorine used and pharmaceutically acceptable salts thereof such as socilium hydromate, and orally administrable dosage forms containing forms of hydrocic acid, for the prevention and/or treatment of diseases such as osteoarthritis, joint effusion, joint inflammation and pain, synovitis, and many other diseases such citated with cartilage degenerating.

[0004] The instant invention also provides gels of hyaluronic acid with carboxymethylcellulose.

BACKGROUND OF THE INVENTION

[0005] Hyahronic acid (HA) exists as a naturally-occuring polysaccharide (also known as a mucuid polysaccharide) that can be extracted from such diverse sources as rooster comb, umbifical cord, vitrous hannet, synovial fluid, pathologic joints, skin and group A and C hemolytic Strolococci. The hyahronic acid is also defined as a high viscosity naturally occurring glycosaminoglysen having oplymeric structure containing alternating N-acetyl-D-glulinited with β 1-4 bonds and the dissocharide units linked with β 1-3 glycosids bonds. It occurs usually as the sodium salt and has a molecular weight range of about 50,000 to 8x10 Dalions. [9006] Hyalumonic acid is a naturally occurring glycossminoglycan HA is ubtiquitous in the organism, with the highest concentration found in soft connective tissue and joint thiul. It is a constituent of the interchlar matrix of connective tissue that exists in almost all vertebrates. It plays an important role in a number of physiological functions, including protection and labrication of cells, maintenance of the structural integrity of tissues, ransport off molecules and the structural integrity of tissues, ransport off molecules and the structural integrity of tissues, ransport off molecules and hair tention and regulation. The clinical benefits of intraarticular HA in the barse are well possibled.

[0007] Natural Hyaluronic acid is polydisperse in respect of molecular weight and is known to show excellent biocompatibility even when implanted or nijected into the body by virtue of the absence of speckes and organ specifical. However, because of the relatively short to vivo residence time of Hyaluronic acid solution in biological applications, improvements in the persistency of Hyaluronic acid by chemical crosslinking with various chemical modifiers has been attempted to broaden its use for medical materials.

[9008] The isolation and characterization of Hyaluronic acid is described in Meyer et al. J. Biol. Chem. 107, 629 (1934); J. Biol. Chem. 114, 689 (1936); Balazs, Fed. Proc. 17, 1086 (1938); Laurent et al; Biochim. Biophys. Acta 42, 740 (1960). The structure of Hyaluronic acid was chelidated by Weissman et al; J. Am. Chem. Soc. 76, 1753 (1954) and Meyer, Fed. Proc. 17, 1075 (1950).

[0009] Hyaluronic acid is an important component of the intercellular matrix. Specifically, the highest levels are found in the eye and synovial fluid of joints. In joints, its primary role is that of lubrication, reducing pain, and inflammation. in arthritic joints HA is deficient. In regards to the joints, synovial fluid supplies autrition to the articular cartilage and has incomparable functions as a lubricant and a shock absorber. It is clarified that its excellent viscoelastisity heavily owes to one of the main components, Hyaluronic acid. Concentration and molecular weight analyses of Hyaluronic acid demonstrated the concentration and molecular weight of Hyaluronic acid in the synovial fluid from patients with arthritis such as osteoarthritis and chronic articular rheumatism generally tended to be lower than in normal synovial fluid, and the lower concentration and molecular weight of Hyaluronic acid were closely associated with development of locomotor dysfunction and pain attributable to the weaker lubricating action and the weaker protecting action on the surface of the articular cartilage of synovial fluid.

[0010] Degradation of the structures in articular cartilage is a typical characteristic of all diseases resulting in chronic destruction of the joint structures. Examples of such disorders are rheumatoid arthritis, psoriatic arthritis, and osteoarmous characteristic content in the properties of the accompanied by destruction of the cartilage, although in most cases this will not develop into the chronically destructive disease. It is not known which factors are crucial for the acutely influenced point to either proceed to healing or develop into the chronic process. Examples of diseases involving scute joint inflammation are yersinia arthritis, prophosphate arthritis, gout arthritis (arthritis urica), soptic arthritis and various forms of arthritis of transition circles are considered and arthritis of the carthritis and various forms of arthritis of transitie circles), soptic arthritis and various forms of arthritis of transmist circles are carthritis and various forms of arthritis of transmist circles are carthritis and various forms of arthritis of transmist circles are carthritis and various forms of arthritis of transmist circles are carthritis and various forms of arthritis of transmist circles.

[0011] Among other factors potentially conducive to the destruction of articular cartilage may be mentioned, for

instance, treatment with cortisone; this has been known for a long time to accelerate the degenerative process in osteoarthrosis.

[6012] Such a so-called "steroid arthropathy" occurs far too often as an undesirable side effect of intra-articular cortisone treatment and can be avoided only by providing for a sufficiently long period of rest after the treatment. Steroid arthropathy is characterized by an advanced degree of articular destruction and X-ray-detectable changes of the same type as occur in advanced degenerative articular disease (Nizolck, D H & White, K K, Cornell Vet. 1981, 71:355-75). According to what is at present accepted as an explanation of the degenerative arthropathy development following treatment with cortisone, this arthropathy is believed to be caused by a primary effect on the chondrocyte metabolism. It should be noted, however, that the actual conditions prevailing in cases of arthritis with severe inflammation of the joint are of a rather more complex character, since in those cases injection of cortisone appears to have an overall positive effect on the clinical picture.

[9013] Also, it is well known that articular cartilage is composed of about 10% of uver, chondroyets and a cartilage matrix. The major components constituting the articular matrix are collagen and proteoglycan; the proteoglycan having good water retention characteristics is contained in the network of collagen having a reticulated structure. The articular matrix is rich in viscoelasticity and has an important role in reducing the stimulus and load imposed on the cartilage in order to maintain the normal morphology and function of the articular cartilage.

[0914] Osseouthrikis and rheumatoid arthritis are representative of the diseases accompanied by the destruction of the cartilage matrix. It is thought that the destruction of the term of the cartilage matrix is those dissues is triggered by mechanical stresses with aging in the case of osteoarthritis and by excess proliferation of the surface layer cells of the synovial membrane, pannus formation and inflammatory cell inflictation in the case of rheumatoid arthritis, and both phenomena are caused through the induction of proteases. Since the degradation of articular cartilage is progressed in the extra-cellular region at a neutral pH, it is said that a matrix metallogroteses (hereinafter referred to as "MMP" or "MMP" when used as the general term) whose optimal pH is in the neutral range plays a beding role in the degradation.

[9015] No medical cure exists for osteoarthritis. The progressive degeneration of the joint due to osteoarthritis is inversible. Present therapies are directed to palliafive medical therapies to reduce inflammation and pain and surgical therapies to reconstruct an affected joint or, in severe cases, to replace the joint with an artificial, prosthetic ioint

[9016] Injection of high molecular weight Hyalmonia said solution into diseased joints has been widely adopted as an effective measure for ostoorthritis among those articular diseases, and the source of high parity HA preparations for this purpose is cockscombs. Such IIA preparations from cockscombs are biologically inherent and quite safe but usually have to be administered as frequently as several to 10 times to show significant therapeutic effect. Persistency tests on rabbits exceeded that HA with a molecular weight of less than 1000000 administered into the knee joint cavities disappeared from the knee joint existies.

suggested the need of frequent administrations (Blood Coagulation and Fibrinolysis, vol 12, 173,1992).

[9017] On the other hand, the molecular weight of HA found in the living body is reported to be as high as millions to 10000000, and a crosslinked HA derivative obtained by treatment with a chemical crosslinker has been developed as a therapeutic agent for knee joints with the idea that high molecular weight HA closer to the biologically instead on kiloly to have higher effect. Reportedly, the crosslinked HA persisted for a period as long as 20 to 30 days after administration into rabbit here joint cavities in the above-mentioned presistency tests and produced sufficient effect when administration into rabbit here in clinical tests, and is practically used as a therapeutic agent for arthritis (Journal of Rheumatology vol.20, 16, 1993).

[9018] A need exists for an effective palliative medication for the treatment of osteoarthritis and other joint diseases which is both safe and effective when used for both shortterm and long-term therapy and which can be administered orally.

OBJECTS OF THE INVENTION

[0019] It is a first object of the present invention to provide a method for treating mammals having joint diseases by oral administration of hyaluronic acid and salts thereof.

[0020] It is another object of the instant invention to provide novel chondroprotective/restorative compositions.

[0021] A further object of the invention is to provide a novel chondroprotective/restorative composition containing hyaluronic acid in paste or gel form.

[9022] A still further object of the invention is to provide novel chondroprotective/restorative compositions containing hyduronic acid, glucosamine sulfate and chondroitin sulfate.

[0023] An additional object of the invention is to provide chondroprotective/restorative compositions containing hydromic acid and bioeffective materials.

[0024] A still additional object of the invention is to provide chondroprotective/restorative compositions containing hyaluronic acid, vitamins and minerals.

[0025] An additional object of the present invention is provide chondroprotective/restorative compositions containing hyaluronic acid, vitamins and minerals.

[0026] Another main object of the present invention is to provide an aqueous gel containing hyafuronic acid and molasses.

[0027] Another object of the present invention is to provide paste formulations containing hyalutonic acid, glucosamine sulfate and molasses.

[9928] An additional object of the invention is to provide gel formulations containing HA in a carboxymethylcellnlose base.

[0629] A further object of the invention is to provide animal feeds containing hyaluronic acid.

[0030] These and other objects of the invention will become apparent from the description hereinafter.

SUMMARY OF THE INVENTION

[0031] The present invention provides a method for teating or preventing noteoarthicit, joint effusion, joint inflammation and pain, synovitis, lameness, post operative arthroscopic sungery, deterioration of proper joint function, the reduction or inhibition of metabolic activity of chondrocytes, the activity of enzymes that degrade cardiage, the reduction or inhibition of the production of hysbaronic acid, said method comprising orally administering to a manufalian species a thorspoutcally effective amount of hysbaronic acid or pharmaceutically acceptable salts thereof.

[0032] The invention is also directed to a Chondroprotective/Restorative composition comprising Hyaluronic Acid or its pharmaceutically acceptable salts and optionally a pharmaceutically acceptable carrier.

[0033] The instant invention also provides a Chondroprotective/Restorative composition comprising; (a) an effective amount of Glecosamine sulfate; (b) an effective amount Hyaluronic Acid or pharmacontically acceptable salts thereof; and (c) optionally a pharmaceutically acceptable earlier.

[0034] Additionally, the invention provides a Chondroprotective/Restorative composition comprising; (b) an effective amount of Chondrolitis sulfate; (b) an effective amount of Hyaluronic Acid or pharmaceutically acceptable salts thereof; and (c) optionally a pharmaceutically acceptable carrier.

[0035] The instant invention further provides a Chondroprotective/Resorative composition comprising; (a) an effective amount of Ghucosamine sulfate; (b) an effective amount of Chondroitin sulfate; (c) an effective amount of Hysluronic Acid or pharmaceutically acceptable salts thereof; and (d) optionally a pharmaceutically acceptable carrier.

[9036] The Chondroprotective/Restorative compositions of the invention further include nutritionally effective amounts of a supplement selected from the group consisting of vitamin A, D and E, ascorbic acid, biotin, pandrothenic, choline, naicin, pyridoxies, ribofaviro, thiamine, calcium, phosphorus, NxCl. copper, front, manganese, iodine, zinc and combinations thereof.

[0037] The invention is also directed to an animal feed having Chondroprotective/Restorative benefits comprising: (a) a mutitionally effective feed base selected from the group consisting of grains, proteins and fats; and (b) an effective amount of Hyaluronic Acid or pharmacoutically acceptable salts thereoff.

[9038] Furthermore, the invention relates to a therapeutic Chondroprotective/Restorative composition comprising: (a) Hyalutomic Acid or its pharmaceutically acceptable salts; (b) a therapeutic drug; and (c) optionally a pharmaceutically acceptable carrier.

[0639] The invention is also directed to a Chondroprotective/Restorative composition in paste form comprising: (a) an effective amount of Hyaluronic Acid or its pharmaceutically acceptable salls; and (b) a sufficient amount of molasses to make a paste.

[0040] Additionally, the invention also relates to a Chondroprotective/Restorative composition in gel form comprising: (a) an effective amount of Hyaluronic Acid or its pharmaceutically acceptable salts; and (b) a sufficient amount of carboxymethylcellulose to make a paste.

DETAILED DESCRIPTION OF INVENTION

[9041] In the first preferred embediment of the invention, there is provided viscosupplementation of joints by oral administration of sodium byalmonate (HA) to mammals and more in particular to racing thoroughbuck. Applicant's conducted a double blind placeba-controlled study wherein ten horses were randomly chosen and given as oral gel (also known as Conquer and containing 100 mg of hyalmoric acid) for 59 days. Every parameter used to measure soundness was improved in the HA treated group. Also, every parameter used to measure routine maintenance of the racing Throughbord was improved in the HA treated group. All horses in the treated group with pre-existing conditions showed clinical improvement during the study.

[0042] In conducting our study, ten actively training Thoroughbreds were randomly selected. Five were given a placebo gel and five were given a gel containing 100 mg of Sodium Hyaluronate. The duration of the study was 59 days. The ages of the horses varied: one two-year old, five three-year olds, two four-year olds, and two five-year olds. Because the half-life of circulating HA is two days or less, the horses were given 100 mg once daily. Upon completion of the study, training and veterinary records were evaluated. Number of days to the track was compared to number of days walked. In addition, horses receiving NSAIDS during the study for any reason were recorded as were horses examined for any lameness. Horses were evaluated weekly for joint effusion, pain on flexion, and signs of lameness. Horses radiographed due to lameness were recorded. Horses with pre-existing conditions were monitored and periodically evaluated.

[6043] The results of oral administration of HA are listed in Tables 1 and 2 below. Treated horses went to the track more days than the non-treated group (40 versus 32). Horse 110, of the non-treated group sustained a cortical stress fracture 33 days into the study. With this non-articular injury removed from the study, the average days to the track of the non-treated group changes from 32 to 35 days. All of the non-treated horses were examined for lameness at some time during the study. None of the treated horses were examined for lameness. All horses in the treated group with preexisting conditions improved. NSAIDS, primarily phenylbutazone, was used at some time during the study in 5 of 5 of the non-treated horses. Less was used in the treated group, 2 of 5. None of the treated group were radiographed during the study while 3 of 5 of the non-treated group had radiographs taken. More horses developed new signs of synovial effusion in the non-treated group, 3 of 5, than in the treated group, 1 of 5. The treated group required less bandaging (3 of 5) than the non-treated group (5 of 5).

TABLE 1

| Horses | Age | Sex | Days To Track | Daya Walked | Examined For Lameners | NSAIDS | Radio- graphed |
|--------|-----|-----|---------------------|----------------|-----------------------------|--------|-------------------|
| | | | TRE | ATED H | ORSES | | |
| 101 | 5 | G | 45 | 14 | NO | YES | NO |
| 102 | 2 | F | 41 | 18 | NO | NO | NO |

TABLE 1-continued

| Horses | Age | Sex | Days To Track | Days Walked | Examined For Lamoness | NSAIDS | Radio- graphed |
|--------|-----|-----|---------------------|----------------|-----------------------------|--------|-------------------|
| 155 | 4 | М | 38 | 23 | NO | NO | NO |
| 196 | 5 | м | 31 | 28 | NO | NO | NO |
| 109 | 4 | M | 46 | 13 | NO | YES | NO |
| | | | TRE | ATED T | TALS | | |
| N/A | N/A | N/A | 201 | 94 | NONE | 2/5 | NONE |
| | | | (Ave. | (Ave. | | | |
| | | | 40) | 19) | HORSES | | |
| | | - | NON-1 | REALBL | HORSES | | |
| 103 | 3 | C | 44 | 25 | YES | YES | NO |
| 104 | 3 | C | 19 | 40 | YES | YES | YES |
| 107 | 3 | P | 43 | 16 | YES | YES | NO |
| 108 | 3 | C | 34 | 25 | YES | YES | YES |
| 115* | 3 | C | 19 | 40 | YES | YES | YES |
| | | _ | NON-1 | REATER | TOTALS | | |
| N/A | N/A | N/A | 159 | 136 | 5/5 | 5/5 | 3/5 |
| | | | (Ave. | (Ave. | | | |
| | | | 32) | 27) | | | |

*Horse 110 sustained a cortical stress fasciure 33 days sate the study. By removing him from the totals the average days to the track becomes 35 days instead of 32 days.

[0044]

TABLE 2

| Honse | Pre- existing Condition | Condition | Improved | New Joint Effusion During Study | Location |
|-------|-------------------------------|------------------------|------------------|--|----------|
| | | TREATED | HORSES | | |
| 101 | YES | Oselete | YES | NO | N/A |
| 102 | NO | N/A | N/A | YES | CARPUS |
| 305 | YES | Severe T Shorth Eff | YES | NO | N/A |
| 106 | YES | Chronic Osslets | YES | NO | N/A |
| 109 | YES | Ossieta NON-TREATI | YES FD HORSES | NO | N/A |
| 103 | YES | Stiffnoss Behind | YES | YES | Съгрия |
| 104 | NO | N/A | N/A | NO | N/A |
| 107 | NO | N/A | N/A | YES | Feriocks |
| 108 | YES | Left Prost Screness | NO | YES | Stiffes |
| 110 | NO | N/A | N/A | NO | N/A |

[6045] As can be appreciated from Tables 1 and 2, borses maintained on a daily dose of cral sodium hyaluronate showed improvement of all soundness characteristics measured. Horses with pre-existing synovitis improved while on oral HA. Accordingly, the data suggests that Oral sodium hyaluronate appears to be effective in preventing lamours in the rating! Thoroughtort Alone of the horses in the treated group, were examined for lamoness which were subtle and difficult to diagnose with diagnostic nerve blocks, one horse became painful in his back and front feet and a fourth horse became artifully lamoness with a diagnostic nerve who will be a feet of the diagnose with diagnostic nerve which is the control of the diagnose with diagnostic nerve blocks therefore a bone scan was performed. Results showed increased uptake in the loft carpa, left front fettlock, and

solar margins of the foot. After resting about 30 days, this horse resumed training. The present invention provides evidence of HAYs ability to have a performance enhancing effect in the racing. Thoroughbred when used orally. In addition, oral administration of HA is effective in the treatment of synovitia associated with osteoarthritis.

[0046] In the second preferred embodiment of the invention, an oral preparation containing sodium hyaltronate was evaluated in the treatment of aseptic synovitis. Horses chosen had clinical signs of joint disease and were treated with 100 mg of Sodium Hyaltronate, 1 g Chondroitin sulfate, and 200 mg Vitamin C for 30 days.

[0047] In conducting the above study, six adult horses were administered 100 mg of sodium hyalturonate, 1 g of Chondroitin sutfate, and 200 mg Vitamin C daily in an oral preparation. The horses were treated for 30 days and were monitored continuously. Clinical evaluations were performed on day 1, day 30, and at day 45 (two weeks after discontinuation of treatment). Clinically, four horses had significant asceptic sayovitis of the metacapophalangual joints. One horse suffered from villinodular synovitis and one horse had degenerative joint disease of the proximal interphalangual joint (fingbone). The results of the study are summarized in Table 3 below.

TABLE 3

| Symptom | Day 1 | Day 30 | Day 45 |
|-----------------------|--------------------------------------|------------------------------|------------------------------|
| Overall evaluation | Inflammed offusion Poin on Sexion | Improved in 5 of 6 borner | Improved in 5 of 6 horses |
| Swelling effusion | 6 of 6 horses | Improved in 5 of 6 homes | Improved in 5 of 6 horses |
| Joint Pain | 6 of 6 horses | Improved in 5 of 6 houses | Improved in 5 of 6 horses |
| Lamouess | Grade 1 or 2 lame in 6 of 6 horses | Sound in 5 of 6 horses | Sound in 5 of 6 horses |
| Hange of | Decreased in 6 of 6 | Improved in 5 of 6 | Improved in |
| Metion | poises. | bosses | 5 of 6 horses |

[9048] As can be appreciated from Table 3, significant improvement was seen in five of six hortess. The amount of synovial effusion and inflammation decreased in all but one case. There was improvement of lameness and decreased pain on flexion. The horse diagnosed with degenerative joint disease of the proximal interphalangeal joint showed no improvement. Oral delivery of sodium bylatronate is a viable alternative for treatment of synovitis in the horse. It is very safe with no side effects being reported in this study.

19049] In a third embodiment of the invention, another ong gle consisting of 100 mg per dose of sodium hyshuronate was evaluated. Horses chosen had significant signs of sprovisis and joint pair. Treatment was continued for 21 days. In conducting the study, four wearding Thoroughbert actions were given 100 mg daily of sodium hyshuronase in a gel formation. All thores were dispussed with moderate to see the conduction of the conductive of the

flexion and lameness was significantly worsened following fettock flexion tests. Radiographs of the affected fetlocks did not reveal any bony abnormalines. Preatment was continued for 21 days and all horses wee evaluated weekly. No other treatments were administered during this time.

[0050] The results are summarized in Table 4. In one foal with effusion in all four fetlocks (Grade 1/5 lame), significant improvement was seen after seven days of treatment. Synovial effusion had decreased and the foal was sound at a walk and trot. Slight lameness was observed after fetlock flexion. By week two, this foal's joints were considered normal and no pain on flexion or lameness could be detected. In the second foal with marked effusion in all four fetlocks (Grade 2/5 lame), moderate synovial effusion was still present at seven days. After fettock flexion, this foal's lameness worsened to a Grade 4/5. At the 14th day exam, significant improvement was observed. The amount of joint swelling had decreased dramatically and the foal's lameness was improved. There was lameness pain on flexion and the lameness after fetlock flexion improved to a Grade 1/5. At the 21st day exam, the joints were considered normal and the foal was sound at a walk and trot. The third and fourth foals with synovial effusion in the front fetlocks showed significant improvement in seven days. They continued to have slight pain on flexion and slightly lame after fettock flexion. By 14 days these foals had slight effusion but were sound and negative to fetlock flexion. At the 21st day exam they were considered normal. The 3 year old racehorse had a significant decrease in synovitis at day 7. By the 14th day there was slight effusion and no pain on flexion. At 21 days, there continued to be slight effusion but no lameness or pain on flevion

levels were 0.1-0.5 mg/Kg of body weight. At least a 58% improvement was observed on their knee joints.

[9053] It should be noted that in treating mammals the recommended daily dosage for hyaluronic acid is about 0.1 to 0.5 mg/Kg of body weight. Accordingly, for a human flue dosage ranges can be from 7 to 40 mg, while for a horse the range can be from 50-250 mg and for a dog the ranges would be 2-8 mg.

[0054] In a fourth embodiment, the invention also provides choodroprotective and restorative compositions which are very useful for oral administration. The compositions contain 10 to 2000 mg of hyaluronic acid and optionally a pharmaceutically acceptable carrier.

[0055] In a fifth embodiment, the pressut invention relates to chondroprotective and restorative compositions useful for oral administration containing; (a) 0.01-10 wt % hysluronic acid or its pharmaceutical acceptable salus; (b) optionally 20-60 wt % glucosamine or its pharmaceutically acceptable issts; (c) optionally 1-15 wt % chondroitin or its pharmaceutical acceptable salus; (d) optionally mutrilionally effective (recommended daily allowance) sucounts of a supplementative (re

[0056] The pharmaceutical acceptable salts of hyaluronic acid include the alkali metal salts as well as the alkaline

TABLE 4

| IABLE 4 | | | | | | | |
|---------|---|--|---|--|--|--|--|
| Horse | Day 1 | Day 7 | Day 14 | Dey 21 | | | |
| #) | Moderate effusion is all four fetlocks. Gmde 1/5 lume/ Moderate pain on flexion | Mild effusion in all four feflock/Sound/Slight pain on flexion | No effusion. Sound/ No pain on flexion | No effusion, Sound/No pain on Sexion | | | |
| #2 | Severe offusion in all four Federicks Grade 2/5 issue, Severe pain on fination | Moderate effusion in all four fetlocks, Grade 1/5 jame fetlocks, Moderate pain on flexion | Mild effusion in front Grade 1/5 lame Moderate pain on flexion | Sjight effusion in front fetlocks, Sound, Slight pain on flexion | | | |
| #3 | Moderate effusion on front Retlocks. Grade 1/5 tame, Mild pair on flexion | Mild effusion is front Fetlocks, Sound, Mild pain on flexion | Slight effection in front Fetlock. Sound, No pain on flexion | No effusion, Sound No pain on fistion | | | |
| #4 | Maderate effusion on front Fotlocks. Grade 1/5 tame, Mild nais on Sexion | Mild offusion in front Petiodes, Saund, Mild pain on flexion | Slight offesion in front Fetlock. Sound, No pain on flexion | No effusion, Sound No pain on flexion | | | |
| ės. | Moderate effusion in front Fetlucks, No Lameness, Mild pain on flexion | Mild affusion in from Petiories. Sound, slight pain on flexion | Slight effusion in front Fetlock. Sound, No pain on flexion | No effusion, Sound No pain on flexion | | | |

^{*}Three year old racehorse

[9051] In a further clinical trial of the invention, 24 hockey highers were treated via oral administration with a combination of sodium hyshronate and chondrottin sulphate in gel form as exemplified in Example 16 for three months. The dosage levels were 0.1-0.5 mg/Kg of body weight. A greater than sixty five percent improvement in their knee joint was observed.

[0052] Additionally, 27 human patients were treated via oral administration with a combination of sodium hyaluronate and chondrollin sulphate in gel form as exemplified in Example 16 for three months after knee surgery. The dosage earth metal salts. Typical salts include sodium hyaluronate, potassium hyaluronate, magnesium hyaluronate and calcium hyaluronate. The preferred salt in the compositions of the invention is sodium hyaluronate.

[9057] The pharmaceutically effective salts of glucosamine are selected from the group consisting of glucosamine chloride, glucosamine bromide, glucosamine iodide and glucosamine sulfate. Similarly, with chondroitin the same type of salts are usable i.e., chondroitin chloride, chondroitin bromide, chondroitin sulfate and chondroitin iodide. [0058] The bio-effective or drug component of the invenion is selected from the group consisting of angiotensin converting enzyme inhibitors, anti-submatics, anti-cholernolmics, anti-cholernolmics, anti-choresants, anti-darrhea preparations, anti-tinctives, anti-inflammatory agents, anti-unseants, anti-stocke agents, anti-unseants, anti-stocke agents, anti-unseants, anti-stocke agents, anti-unseants, anti-stocke agents, anti-unseants, anti-tonic drugs, amino-acid preparations, anti-uncides, anti-obseively drugs, anti-prastitises, anti-protection, anti-protection and anti-protecti

[0059] The bio-effecting agent is selected from the group consisting of acetaminophen, acetic acid, acetylsalicylic acid, buffered acetylsalicylic acid, albuterol, albuterol sulfate, ethanol isopropunol, allautoin, aloc, aluminum acetate, aluminum carbonate, aluminum chlorohydrate, aluminum hydroxide, alprozolam, amino acids, aminobenzoic acid, amoxicillin, ampicillin, amsacrine, amsalog, anethole, aspartame, stenoloi, bacitracin, balsam peru, beclomethasone dipropionate, benzocaine, benzoic acid, benzophenones, benzoyl peroxide, hiotin, bisacodyl, bornyl acetate, bromopheniramine maleate, buspirone, calleine, calamine, calcium, calcium carbonate, calcium casinate, calcium hydroxide, camphor, captopril, cascara sagrada, castor oil, Cephalosporins, cefaclor, cefadroxil, cephalexin, cetylalcohol, cetylpyridinium chloride, chelsted minerals, chloramphenicol, chlorcyclizine hydrochloride, chlorhexidine gluconste, chloroxylenol, chloropentostatin, chlorpheniramine maleate, cholestyramine resin, choline bitartrate, cimetidine hydrochloride, cinnamedrine hydrochloride, citalopram, citric acid, Clenbuterol, cocoa butter, cod liver oil, codeine and codeine phosphate, clouidine, clouidine hydrochloride, clorfibrate, ciprofloxacin HCl, cyanocobalamin, cyclizine hydrochloride, DMSO, danthron, Dantrium, dexametbazone, dexbrompheniranime maleate, dextromethorphan hydrobromide, diazapam, dibucaine, diclofenac sodium, digoxin, dilnazem, dimethicone, dioxybenzone, diphenhydramine citrate, diphenhydramine hydrochloride, docusate calicum, docusate potassium, docusate sodium, doxycycline hyclate, doxylamine succinate, efaroxan, enalapril, enoxacin, erythromycin, estropipate, ethinyl estradiol, ephedrine, epinephrine bitartrate, erythropoletin, eucalyptol, ferrous fumarate, ferrous gluconate, ferrous sulfate, folic acid, fosphenytoin, Flunixin Meglumine, fluoxetine HCl, furosemide, gabapentan, gentamicin, Gentocin sulfate, gemfibrozil, glipizide, glycerin, glyceryl stearate, griscofulvin, guaifenesin, hexylresorcinol, hydrochlorothiaxide, hydrocodone bitartrate, hydrocortisone, hydrocortisone acctate, 8-hydroxyquinoline sulfate, ibuprofen, indomethacin, inositol, insulin, iodine, ipecac, iron, isoxicam, ketamine, Ketofin, koalin, lactic acid, lanolin, lecithin, lidocaine, lidocaine hydrochloride, lifinopril, liotrix, lovastatin, MSM (methylsulfonylmethane), magnesium carbonate, magnesium hydroxide, magnesium salicylate, magnesium trisilocate, melenamic seid, meclofenanic seid, meclofenamate sodium, medroxyprogesterone acctate, methenamine mandelate, Methocarbamol, menthol, meperidine hydrochloride, metaproserenol sulfate, methyl nicotinate, methyl salicylate, methylcellulose, methsuximide, metromidazole, metromidazole hydrochloride, metoprolol tartrate, miconazole

nitrate, mineral oil, minoxidil, morphine, naproxen, naproxen sodium, nifedipine, neomycin sulfate, Neomycin-Bacitracia, niacia, niacinamide, nicotine, nicotinamide, nitroglycerin, nonoxynol-9, norethindone, norethindone acetate, nystatin, octoxynol, octyl dimethyl PABA, octyl methoxycinnamate, omega-3 polyunsaturated fatty acids, omeprazole, oxolinic acid, oxybenzone, oxtriphylline, paraaminobenzoic acid (PABA), padimate O, paramethadione, Penicillin, pentastatin, peppermint oil, pentaerythriol tetranitrate, pentobarbital sodium, pheniramine maleate, phenobarbital, phenol, phenolphthalein, phenybutazone, phephenylpropanolamine, nylephrine hydrochloride, phenylpropanolamine hydrochloride, phenytoin, phenelzine sulfate, pirmenol, piroxicam, polymycin B sulfate, potassium chloride, potassium nitrate, prazcpam, prednisone, prednisolone, procainamide hydrochloride, procaterol, propoxyphene, propoxyphene HCl, propoxyphene napsylate, pramiracetin, pramoxine, pramoxine hydrochloride, propropolol HCl, pseudoephedrine hydrochloride, pseudoephedrine sulfate, pyridoxine, quinapril, quinidine gluconate, quinestrol, ralitoline, ranitadine, resorcinol, riboflavin, salicylic acid, sesame oil, shark liver oil, simethicone, sodium bicarbonate, sodium citrate, sodium fluoride, sodium monofluorophosphate, Sulfa-drugs, sulfanethoxazole, sulfur, tacrine, tacrine HCl, theophylline, terfenidine, thioperidone, trimetrexate, triazolam, timolol maleate, tretinoin, tetracycline hydrochloride, tolmetin, tolnaflate, triamcinilone, triclosan, triprolidine hydrochloride, undecylenic acid, vancomycin, verapamil HCl, vidaribine phosphate, vitamin A, vitamin B, vitamin C, vitamin D, vitamin E, vitamin K, witch hazel, xylometazoline hydrochloride, zinc, zinc sulfate, and zinc undecylenate.

[0060] The compositions of the invention can be made in paste form, gel forms, tablets and capsules. The paste form of the invention contains molasses in an amount effective to form a paste.

[9061] The gel forms of the invention are formed by mixing the actives with water and then adding a gelling agent. The gelling agent is selected from the group consisting of cellulase or a cellulose derivative in an amount of from 3.5 to 5 wt., and said cellulose derivative is selected from the group consisting of hydroxypropyl methyl cellulose, hydroxypropyl cellulose, hydroxypropyl cellulose, cyloroxypropyl cyloroxypro

[9062] In making the compositions of the invention, the active materials will usually be mixed with a carrier, or diluted by a carrier, or enclosed within a carrier which may be in the form of a carsuals, aschet, paper or other container. When the carrier serves as a dilutent, it may be solid, semi-solid or liquid material which acts as a vehicle, excipient or medium of the derive ingredient. Thus, the compositions can be in the form of tablets, pills, pseuders, lozanges, scalets, cachese, clixis, suspersions, enulsions, solutions, syrups, aerosols (as a solid of in a liquid medium), obtiments containing for example up to 10% by weight of the active compound, soft and hard gelalin capsules, surpositories, storile injectable solutions and sterrile packaged prowders.

[9063] Some examples of suitable carriers, excipients, and diluents include factore, dextrose, sucrose, sorbitol, manni-

tol, starches, gum acacia, calcium phosphate, alginates, rapacache, pelatin, calcium silicate, microrystaline cellulose, polyvinylpyrrolidone, cellulose, water, syrun, methyl-celluse, methyl and propyllydroxybenzoates, talc, magnesium stearate and mineral oil. The formulations can additionally include lubricating agents wetting sgents, remaistrying and suspending agents, preserving agents, weetening agents or flavoring agents. The compositions may be formulated so as to provide rapid, sustained or delayed release of the active ingredient after administration to the patient by employing procedures well-know in the art.

[6064] In a sixth embodiment of the invention, an animal feed is provided having chondroprotective and restorative properties. The animal feed base of the present invention comprises farinaceous material selected from the group consisting of wheat, wheat flour, wheat meal by-products and corn in an amount of 25 to 70% by weight based on the total weight of the feed, further comprising proteinaceous material selected from the group consisting of soybean meal, soy flour, peanut meal, cottonseed meal, safflower seed meal in an amount of from 5 to 40% by weight based on the total weight of the feed, further comprising fibrous material selected from the group consisting of soy hulls, cottonseed halls, rice halls in an amount of from about 2 to 35% by weight based on the total weight of the feed, further comprising nutritional supplements selected from the group consisting of vitamin A, D and E, ascorbic acid, biotin, panthothenic, choline, niscin, pyridoxine, riboflavin, thiamine, calcium, phosphorus, NaCl, copper, iron, manganese, iodine, zinc and combinations thereof, in an amount of from 3 to 4% by weight based on the total weight of the feed, further comprising a vegetable oil coating, said oil selected from the group consisting of soybean oil, corn oil, safflower oil, cottonseed oil, peanut oil, in an amount of from 1 to 15% by weight based on the total weight of the feed.

[0965] The above feed base is blended with a paste having the following formulation ranges: (a) 0.01-10 wt % hyaluronic acid or its pharmaceutical acceptable salts; (b) optionally 20-60 wt % glucosamine or its pharmaceutically acceptable salis; (c) optionally 1-15 wt % chondroitin or its pharmaceutical acceptable salts; (d) optionally nutritionally effective (recommended daily allowance) amounts of a supplement selected from the group consisting of vitamin A, D and E, ascorbic acid, B complex, B12, B1, biotin, panthothenic, choline, nincin, pyridoxine, riboflavin, thiamine, calcium, phosphorus, NaCl, copper, iron, manganese, iodine, zinc and combinations thereof; (e) optionally effective amounts of a bioactive agent or drug; and (f) 15-35 wt % molasses. The feed of course is formulated in way to provide optimum nutrition and optimum chondroprotection depending on the specific animal and their current state of bealth.

[9066] The present invention is the most unique chompotectice/restorative agent available. The molasses flavored oral paste provides a practical, efficient, and efficient means of administration orally or top dressing feed. When added to the feed, the molasses base binds to the feed to insire total consumption. When necessary, an easy messable dose can be administered orally. The highly palsable formulation of the invention is the first to combine high levels of (flucosamine salifae (GS) with Chondroith sulfate (CS) and Hyaluronic Acid (HA) in an easy to absorb, low molecular weight formula. It has also been shown that liquid

or paste forms are more readily absorbed than encapsulated or powder forms. The chondroprotective/restorative agent of the invention enhance chondrocyte synthesis, increase synthesis of hyalutronic acid, inhibit enzymes that degrade cartilage, and reduce pain and synovitis. It must also slow down or reverse progression of the disease. The present invention, with it's unique combination of GS, CS, and HA is the closest yet to satisfying these criteria.

[9067] These three substances are the three connective tissue molesules needed to rebuild and synthesize new tissue. Commertive tissue is mainly of collagen and proteoglycans. Percoglycans provide the framework for collagen and hold water, enhancing the flexibility and resistance to compression needed to counteract physical stress. The building blocks for all proteglycans are amino sugars. Chrocosumine is the building block needed as the precursor for all subsequent amino sugar symbesis. The formation of N-acertylghocosamine, chondroit suffate, and bylauronic acid require glucosamine for their synthesis. In fact, glucosamine makes up 50% of the hyaluronic acid molecule.

[8068] Glucosamine sulfate along with Chondroitin sulfate have become very popular supplements administered in the treatment of degenerative joint disease. Recent studies have questioned whether the combination produces better results than Glucosamine sulfate alone. Also there is much debate over which glucosamine salt is preferred. Embodiments of the present invention utilize Glucosamine sulfate as it's source of Glucosamine. Most of the past and present research has been performed on the sulfated form. There is evidence that suggests that a component of the activity of GS and CS is related to the sulfate residues found in these compounds. Sulfur is an essential nutrient for the stabilization of the connective tissue matrix. It has been proposed that the sulfate molecules of GS and CS contribute to the therapeutic benefits of the compounds in generative joint disease. If this is true, it would suggest that GS, as opposed to N-acetylglucosamine and glucosamine HCl, is the best form of glucosamine supplementation. Recently, it has been shown that high-dose glucosamine may provide rapid symptomatic benefit and in the longer term and the repair of damaged cartilage. The high dose of glucusamine non only promotes synthesis of cartilage proteogycans, but stimulates synovial production of hyaluronic acid. This would explain the anecdotal reports that a high dose of glucosamine is

[0069] As previously explained, the present invention comprises a highly palatable formulation, which is the first to combine high levels of Glucosamine sulfate (CS) with Chondroitin sulfate (CS) and Hyaluronic Acid (HA) in an easy to absorb, low molecular weight formula.

[6070] Cliucosamine, which is formed in the body as glucosamine 6-phosphate is the most fundamental building black required for the biosynthesis of the classes of compounds such as glucolipids, glycoproteins, glycosamine glycosamine plays a role in the formation of articular glucosamine plays a role in the formation of articular surfaces, tendons, ligaments, synovial fluid, skin, bone, heart valves, blood vessels and mucus secretions of the digestive, respiratory and unitary tracts. Glucosamine sufface is greater than 90% absorbed and is quickly incorporated into articular cartilage following onal administration.

[9671] In one study, no LD50 was established for Glucosamine sulfate since even at very high levels (5000 mg/kg orally) there was no mortality in mice and rats. While treatment with GC does not produce the initial dramatic reductions in pain normally associated with NSAIDs, it's ability to reduce pain is consistent and progressive turous out the course of it's administration, resulting it a long-term improvement in the condition. Glucosamine is a small molecule and is very soluble in water.

[6072] Chondroith Sulfate achieves benefits much more slowly than glucosanine. Chondroith bioavalability following oral administration is around 15%. Because of its lower availability, the time needed to see a clinical response is lengthened. Chondroitin improves join fluidity by drawing water to the cartilage, it is accompanied by nutrients which are supplied to the cartilage, a companied by nutrients which are supplied to the cartilage, and the supplied to the cartilage, and the supplied to the cartilage of t

[0073] Hyaluronic acid is one of many glycosaminoglycans of physiological significance. Other are Chondroitin sulfate, Heparin sulfate, and Dermatan sulfate. The HA molecule is very similar to that of Chondroitiu sulfate. In numerous studies, the oral absorption of CS, HS and DS have been well documented. The bioavailabilities range from 15-20%. Hyaluronic acid has been shown to be absorbed through skin and reach the dermal lymphatics. Also, high levels of hyaluronan has been detected in the intestinal lymphatics. In addition, studies have been performed to determine the effects of HA secreted in saliva. Others have looked at hyshironic acid production by oral epithelial cells. According to the present invention, there is a beneficial effect when Glucosamine sulfate, Chondroitin sulfate, and Hyaluronic acid are administered orally. Generally, the oral administration of embodiments of the present composition has a quicker clinical response than is produced when each component of the composition is given individually. A significant difference is an acute or a rapid relief in join pain inflammation and swelling achieved by oral administration of the composition. A dramatic improvement over seven to ten days is achieved whereas it usually takes weeks for that effect to occur. Another benefit received is that of oral preparation and administration of the HA given, for example, in the equine in any formulation. The administration of the HA composition orally and having a clinical effect eliminates more evasive procedures. Other ways to give HA would be more evasive, such an injection by IV or other administration into the joints. Basically, the embodiments of the present invention include oral preparations that are less evasive and also may include an embodiment which is the only oral way to give HA. This provides another alternative to giving it by an injection.

[0074] Another benefit is that embodiments of the present invention, with it's high dose of Ghucusamine sulfate, Hysluronic acid, and Chondroitin sulfate, appears to have a synergistic effect which hastens the clinical response.

[0075] One further embodiment of the present invention is a unique formulation that combines Giucosamine sulfate, Chondrotin sulfate, and Hyaluronic acid into a paste formulation for direct oral administration or top dressing feed. This is the only product available which combines these three substances which are critical for cartilage neutabolism and production of synovial fluid. Also, this embodiment is the only oral paste formulation available for any one of these supplements. Early clinical trials have shown that when the three products are combined, they have a synergistic effect. The clinical effects have been impressive. Data has shown a quicker clinical response when GS, CS, and HA are combined than when they are used individually. Conditions in which embodiments of the present invention would be beneficial:

[0076] 1) Osteoarthritis

[0077] 2) Joint effusion

[0078] 3) Joint inflammation and pain

[6079] 4) Post operative arthroscopic surgery

[0080] 5) Restoring proper joint function

[0081] 6) Promote metabolic activity of chondrocytes (cartilage producing cells)

[0082] 7) Inhibit enzymes that degrade cartilage

[0083] 8) Stimulate the production of Hyaluronic

[0084] Embodiments of the present invention possess the following advantages:

[9085] 1) Only paste formulation

[9986] 2) Only combination of GS, CS, HA in a paste formulation

[0087] 3) Only oral paste form of Glucosamine

[0088] 4) Only oral paste form of Chondroitin

[0089] 5) Only oral paste form of Hyaluronic acid

[0090] 6) Only oral paste in a molasses flavored base

[8091] 7) Only oral gel in apple flavored carboxymethylcellulose base.

[0092] One embodiment of the present invention possesses a molasses flavor. Other flavors would include apple, cherry, and any other palatable flavor. One embodiment of the present invention comprises the following:

| | W: % | |
|-------------------------|-------|--|
| Gluconamine nulfine | 46.03 | |
| Chondroitin sulfate | 4.69 | |
| Sodium Hvalurosete | 6.18 | |
| Managanese sulfate | 6.18 | |
| Powdered sugar | 8.70 | |
| Xamban 2010 | 0.10 | |
| Moiasses | 25.00 | |
| Water | 14.00 | |
| Givesrine | 0.70 | |
| Open Starch | 0.30 | |
| Sodium Benzoste | 0.50 | |

[6093] Embodiments of the present invention in a paste formulation has many advantages. When adding to Food, the formulation will stick to grain to insure total consumption. Embodiments of the past formulation can be given orally (direct administration) or added to feed-depending on man-

- [0094] 1) Better absorption with liquids
- [6095] 2) Molasses flavored paste---more palatable
- [8096] 3) Apple flavored gel-more palatable
- [0097] 3) Sticky consistency—animal cannot spit product from mouth which insures total dose
- [0098] 4) Syringe dose insures more accurate dose.
- [0099] 5) Brown sugar included—more palatable Effects of GS vs CS: Glucosamine sulfate:
- [0100] 1) Enhances chondrocyte synthesis
- [0101] 2) Enhances synthesis of hyaluronic acid
- [0102] 3) Reduces joint pain
- [8103] 4) Reduces synovitis Chondroitin sulfate:
- [0104] 1) Also helps with chondrocyte synthesis
- [0105] 2) C8 has been found to inhibit degradative enzymes in cartilage
- [0106] 3) CS strengthens and enhances vessels that feed joints or supply them with nutrients by reducing arterial plaque and clear cholesterol deposits.
- [0107] 4) Reduces joint pain and improves joint mobility.
- [0108] 5) Reduces synovitis associated with joint arthritis.
- [6109] Neither GS or S fulfills the quest for the ideal chondroprotect/vertocative agent separately but when combined they appear to provide the necessary components for the health and wellbesing of the joint. Hyahronic acid complements the combination by helping to restore the HA levels needed for joint health and habrication which are decreased when synovitis is present.

[0110] Hyaluronic acid is a glycosaminoglycan. Other glycosaminoglycans are Chondroling sulfate, leparin sulfate, and Dermatan sulfate. The most abundant GAG is Chondrolin sulfate. The three related GAGs have been found to be absorbed orally. Because of their chemical similarities and the clinical reports of improvement of syrovinis, HA has a syutengistic effect with GS and CS when given orally. This effect is observed as a more rapid clinical response than then GS and CS are given individually.

[6111] Clinically, responses are seen in 7 to 10 days we three to four weeks or not at all when GS and GS are given without HA. Therefore, we have seen a dramatic decrease in synovitis when HA is combined with GS and CS. This leads us to conclude that HA is absorbed orally and effective either abone or in combination with GS and CS. Therefore, an additional embodiment of the invention comprises a composition including HA and any acceptable carrier, such as the paste formulation disclosed herein and any other liquid, powder, gel or similar type carrier.

[0112] Another embodiment of the invention includes a paste formulation containing the active component iscouprine. Isoxuprine is a vascofflator and is utilized in treatment of many afflictions including the treatment of navicular disease. One effect of isoxuprine is that it stimulates the vasodilator nerves, such as the vaso-inhibitory and vasobypotonic nerves, and causes dilation or relaxation of the blood vessels. Administration of isosuprine to a patient, such as an animal, in the form of a paste is beneficial to ensure adequate administration.

[0113] The present invention is illustrated by the following Examples, but should not be construed to be limited thereto. In the Examples, "part" and "%" are all part by weight or % by weight unless specified otherwise. Examples 1-14 are paste compositions of the invention.

| EXAMPLE 1 | | |
|------------------------|--------|--|
| Component | Wt 16 | |
| Sodium Hyalurosate | 0.144 | |
| Powdered Souar 10X | 60,144 | |
| Olycerise | 0,7 | |
| Nanthae Gum | 9.2 | |
| Sodjum Benzoate | 0.7 | |
| Citric Acid Anhydrous | 0,2 | |
| Molasses | 23,5 | |
| Water Di | 14.4 | |
| TOTAL | 100 | |

| EXAMPLE | 2 |
|-----------------------|--------|
| Component | Wt % |
| Chendroitie Suffate | 4 |
| Sodium Hyaluresate | 0,244 |
| Powdard Sugar 10X | 50.244 |
| Olycerine | 0.7 |
| Xanthan Gum | 0.2 |
| Sodinim Benzoste | 0.7 |
| Citric Acid Aphydrous | 0.2 |
| Molssaga | 29.5 |
| Water DI | 34.4 |
| TOTAL | 100 |

| EXAMPLE 3 | _ | |
|-------------------------|--------|--|
| Component | Wt % | |
| Giucosamine Sulfate | 40.144 | |
| Sodium Hyniuronne | 0.344 | |
| Powdered Sugar 10X | 20 | |
| Glycerine | 9.7 | |
| Xantian Oum | 0.2 | |
| Sodium Benzoste | 0.7 | |
| Citric Acid Anhydrous | 0.2 | |
| Molastes | 23.5 | |
| Water Di | 14.4 | |
| TOTAL. | 100 | |

| | EXAMPLE 4 | EXAMPLE 4 | | |
|-------|-----------------------|-----------|---|--|
| | Component | Wt % | | |
| ***** | Glueosamine Sulfate | 36.144 | • | |
| | Chondroitin Suifate | 4 | | |
| | Sodiam Hysfurosate | 0.344 | | |
| | Powdered Sugar 10X | 20 | | |
| | Glyceriae | 0.7 | | |
| | Xanthan Gum | 0.2 | | |
| | Sodiem Beszoste | 0.7 | | |
| | Citric Acid Anhydrous | 0.2 | | |
| | Molasses | 23.5 | | |
| | Water DI | 16.4 | | |
| | TOTAL | 306 | | |
| | | | | |

| -continued | | -continued | | |
|----------------------------------|--------------|--|-----------------|--|
| EXAMPLE | 5 | EXAMPLE | <u> </u> | |
| Component | Wt % | Component | ₩i % | |
| Glucosamine Sulfate | 36 | Gitscosumine Sulfate | 36 | |
| Sodjum Hyaltsronate | 0.144 | Chondroitin Sulfate | 0.144 | |
| Manganese Sulfate | 0.144 | Sedium Hysiusonate | 0.144 | |
| Powdered Sugar 19X | 24 | Manganese Sulfate | 0.144 200 TO | |
| Givernite | 9.7 | Vitamia D | 20 | |
| Xanthau Gum | 0.2 | Powdered Sugar 16X | 0.7 | |
| | 0.7 | Cityourine | 0.7 | |
| Sedium Benzoele | 0.7 | Xasthan Gum | 9.7 | |
| Citrie Acid Anhydrous | 23.5 | Sodiem Bezzonte | 0.2 | |
| Molasees | | Citric Acid Arrhydrous Molasses | 23.5 | |
| Water DI | 14.4 | Water DI | 14.4 | |
| TOTAL | 100 | TOTAL | 100 | |
| EXAMPLE | 6 | EXAMPLE 1 | | |
| Composent | Wi % | Component | Wt % | |
| Choadroitin Sulfate | 4 | | 36 | |
| Sodium Hyaluronate | 0.144 | Glucosamine Sulfate Chendroltin Sulfate | 30 | |
| Manganese Sulfate | 0.144 | | 5.144 | |
| Powdered Sugar 30X | 56 | Sodium Hyakironate | 5.144 5.144 | |
| Glyceriae | 0.7 | Manganese Sulfate | 200 mg | |
| Xaathan Gum | 6.2 | thupsofen Powdered Sugar 10X | 20 mg | |
| Sodium Benzonia | 0.7 | Powdend Sugar 10X | 0.7 | |
| | | Glycerine | 0.2 | |
| Citric Acid Anhydrous | 0.2 23.5 | Xanthan Gum Sodiem Benzoste | 0.7 | |
| Moisses | | Citrie Acid Aubydrous | 0.2 | |
| Water Df | 14.4 | | 23.5 | |
| | 100 | Melasses Water DI | 14.4 | |
| TOTAL | | TOTAL. | 100 | |
| EXAMPLE | | EXAMPLE : | | |
| Component | W: % | Component | NAVE OF | |
| Glucosamina Sulfate | 36 | | | |
| Chondroitin Sulfate | 4 | Glucosamine Sulfate | 36 | |
| Sodium Hyaluronale | 0.244 | Chondroitin Sulfate | 4 | |
| Manganese Sulfate | 0.344 | Sodium Hynluronate | £144 | |
| Powdered Sugar 10X | 20 | Manganese Sulfate | U.164 | |
| Giycerins | 0.7 | Erythromycia | 200 mg | |
| Xanthan Gum | 0.2 | Pawdered Sugar 19X | 20 | |
| Sodium Benzoste | 0.7 | Glycerine | 07 | |
| Citrie Acid Anhydrous | 9.2 | Xamhae Gum | 0.2 | |
| Moinses | 23.5 | Sodium Beazonte | 0.7 | |
| Water DI | 14.4 | Citric Acid Anhydrous | 0.2 | |
| • | | Molasses | 23.5 | |
| TOTAL | 100 | Water DI | 14.4 | |
| EXAMPL | 8.5 | TOTAL. | 106 | |
| Component | Wt % | EXAMPLE | | |
| Otocosamine Sulfate | 35 | Component | Wi % | |
| Chopdroitin Sulfate | 4 | Glucusamine Sulfate | 36 | |
| Sodinm Hyalwonate | 0.144 | Chandroitin Salfate | 4 | |
| Manganese Sulfate | 0.144 | Sedium Hyakitonate | 6.344 | |
| Vitamia C | 1 | Manganese Sulfate | 0.344 | |
| Powdered Sugar 10X | 20 | Isoxuorine | 100 mg | |
| Givenne | 6.7 | Powdered Sugar 10X | 26 | |
| | 0.2 | Glycerine | 0.7 | |
| Xanthan Cittan | | Xanthan Guer | 0.2 | |
| Sodium Beuzoste | 0.7 | Sodium Benzoste | 0.7 | |
| | 0.2 | Citric Acid Anhydrous | 0.2 | |
| Citric Acid Anhydrous | | | | |
| Giric Acid Anhydrous Molesses | 23.5 | | | |
| | 23.5 34.4 | Molastos Water DI | 23.5 14.4 | |

| -con | |
|------|--|
| | |

| | EXAMPLE 13 | | |
|-----|----------------------|--------|--|
| | Component | W: % | |
| | Blaccesmine Sulfate | 40.344 | |
| | Sodium Hyaluronate | 0.344 | |
| 1 | buprotes | 800 mg | |
| 1 | Pawdered Stress 10X | 20 | |
| - 6 | Ofveering | 0.7 | |
| | Kanthan Gum | 0.2 | |
| | Sodium Benzoare | 0.7 | |
| - 6 | Stric Acid Anhydrous | 0.2 | |
| | Molassos | 23.5 | |
| , | Water DI | 14.4 | |
| | TOTAL. | 100 | |

| EXAMPLE 14 |
|------------|
| |
| |

| Composed | Wt % | |
|---------------------|--|---------------------|
| Gluggsamine Sulfate | 46.03 | _ |
| Choudroitin Sulfate | 4.60 | |
| Sodium Hvalurgasta | 0.18 | |
| Manganose Sulfaie | 0.18 | |
| Powdered Sugar 19X | 8.70 | |
| | 5.7 | |
| | 0.10 | |
| | 6.50 | |
| | 6.30 | |
| Molasans | 25.00 | |
| Water Di | 14.0 | |
| TOTAL | 100 | |
| | Ohoosamine Sulfate Choedroitie Sulfate Sodom Hyslurosate Sodom Hyslurosate Mangasce Sulfate Powdered Sugar IOX Olycarine Xasthan Church Com Salech Molasses Water DI | Chrossemine Sulfate |

EXAMPLE 15

[0114] The following Example is directed to a gel of HA using CMC as the gelling agent.

| Composent | ₩t % |
|-----------------------------------|------|
| Sodium Hyaluronase | 1.00 |
| Sodium Carhoxymethyl cellulose | 1.00 |
| Propylene glyoni | 1.20 |
| Sodium Benzoste | 0.50 |
| Cisric Acid | 0.30 |
| Apple Flavor | 1.5 |
| Water DI | 94.5 |
| TOTAL | 190 |

EXAMPLE 16

[0115] The following Example is directed to a gel of HA and chondroitin sulphate using CMC as the gelling agent.

| Component | Wt % |
|-----------------------------------|------|
| Sodism Hyshronae | 1.00 |
| Chondroitin Sulphate | 4.60 |
| Socium Carboxymethyl cellulose | 1.00 |
| Propylene glycol | 1.20 |
| Sextum Bengouse | 0.50 |

-continued

| ·ccontinuou | | |
|---------------------|--|--|
| W: % | | |
| 0.30 1.5 90.5 | | |
| 100 | | |
| | | |

EXAMPLE 16

[0116] Hard gelatin capsules are prepared using the following ingredients

| Component | Amount ing |
|--------------------|------------|
| Sodium Hyslurogate | 100.00 |
| Starch dried | 200.00 |
| Magnesium steamte | 19.00 |
| TOTAL | 386.00 |

EXAMPLE 17

[0117] Hard gelatin capsules are prepared using the following ingredients

| Component | Amount mg | |
|------------------------|-----------|--|
| Sodium Hyalurosate | 100.00 | |
| Chondroitin sulphate | 200.00 | |
| Statch daied | 200.00 | |
| Magnesings steamte | 10.00 | |
| TOTAL | 510,00 | |

[0118] The above ingredients are mixed and filled into hard gelatin capsules in 510 mg quantities.

EXAMPLE 18

[0119] Hard gelatin capsules are prepared using the following ingredients

| Consponent | Ansutet erg | |
|----------------------------|-------------|--|
| Sodium Hyslurosete | 309,00 | |
| Microcrystalline coliniose | 400.00 | |
| Silicon Dioxide, fumed | 10.00 | |
| Stearie Acid | 5.00 | |
| TOTAL | 310.60 | |
| Stearie Acid | 5.00 | |

[0120] The components are blended and compressed to form tablets each weighing 665 mg.

[0121] While the invention has been described in conjunction with specific embodiments thereof, it is evident that many alternatives, modifications, and variations will be apparent to those skilled in the art in light of the foregoing description. Accordingly, it is intended to embrace all such alternatives, modifications, and variations which fall within the spirit and broad scope of the invention.

What we claim is:

1. A method of treating or preventing ostsoarthritis, joint effusion, joint inflammation and pain, synovitis, laneness, post operative arthroscopic surgery, deterioration of proper joint function, the reduction or inhibition of metabolic activity of chondrocytes, the activity of enzymes that degrade cartiliage, the reduction or inhibition of the production of Hyaluronic actid in a mammal, said method comprising orally administering to said mammal a therapeutically effective amount of Hyaluronic Acid or pharmaccutically acceptable saits thereof.

 The method of claim 1 further including an effective amount of Glucosamine or its pharmaceutically acceptable salts.

 The method of claim 1 further including an effective amount of chondroitin or its pharmaceutically acceptable salts.

 The method of claim 2 wherein said pharmaceutically acceptable salt is glucosamine sulfate.

The method of claim 3 wherein said pharmaceutically acceptable sait is chondroitin sulfate.
 The method of claim 1 further including the acceptable.

The method of claim 1 further including the repentically
effective amounts of glacosamine sulfate and chondroitin
sulfate.

The method according to claim 1 wherein said hyaluronic acid is uncrosslinked.

8. The method according to claim 1 wherein said pharmaceutically acceptable sail is sodium hyaluronate.

9. The method according to claim 8 wherein said therapeutically effective amount of sodium hyahronate is in the range of 10 mg to 2000 mg.

10. A Chondroprotective/Restorative composition com-

 A Chondroprotective/Restorative composition comprising an effective amount Hyaluronic Acid or its pharmaceutically acceptable salts and optionally a pharmaceutically acceptable carrier.

A Chondroprotective/Restorative composition comprising:

(a) an effective amount of Glucosamine sulfate;

 (b) an effective amount Hyaluronic Acid or pharmaceutically acceptable salts thereof, and

(c) optionally a pharmaceutically acceptable carrier.

A Chondroprotective/Restorative composition comprising:

(b) an effective amount of Chondroitin sulfate;

(b) an effective amount of Hyaluronic Acid or pharmaceutically acceptable saits thereof; and (c) optionally a pharmaceutically acceptable carrier.

13. A Chondroprotective/Restorative composition comprising

(a) an effective amount of Glucosamine sulfate;

(b) an effective amount of Chondroitin sulfate;

(c) an effective amount of Hyaluronic Acid or pharmaceutically acceptable salts thereof, and (d) optionally a pharmaceutically acceptable carrier.

14. The Chondroprotective/Restorative composition of claim to further including nutritionally effective amounts of a supplement selected from the group consisting of vitamin A, D and E, assorbic acid, biotin, panthothenic, choline, niacin, pyridoxine, riboflavin, thiamine, calcium, phosphorus, NaCl, copper, iron, manganese, iodine, zine and combinations thereof.

15. The Chondroprotective/Restorative composition of claim 11 further including nutritionally effective amounts of a supplement selected from the group consisting of vitamin A, D and E, ascorbic acid, blotin, panthothenic, chollene, nicin, pyridoxine, ribollavin, thamanine, calchun, phosphorus, NaCl, copper, iron, manganese, iodine, zinc and combinations thereof.

16. The Chordroprotective/Restorative composition of claim 12 further including mutritionally effective amounts of a supplement selected from the group consisting of vitamin A, D and E, ascorbic acid, biotin, panthothenic, choline, nician, pyridoxine, riboflavin, litamine, calcium, phosphorus, NaCl, copper, iron, manganese, iodine, zine and combinations thereof.

17. The Chondroprotective/Restorative composition of a supplement selected from the group consisting of vitamin A. D and E, ascorbie exid, biotin, panhothenic, choline, niciae, pyridoxine, rholdivin, thamine, calcium, phosphorus, NaCl, copper, iron, manganese, iodine, zinc and combination stheroit.

18. An animal feed having Chondroprotective/Restorative benefits comprising:

 (a) a nutritionally effective feed base selected from the group consisting of grains, proteins, fats and mixtures thereof; and

(b) an effective amount of Hyaluronic Acid or pharmaceutically acceptable salts thereof.

The animal leed of claim 18 further including an effective amount of Glucosamine sulfate.
 The animal leed of claim 19 further including an

effective amount of Chondroitin sulfate.

21. The animal feed of claim 20 further including molas-

22. The animal feed of claim 21 further including nutritionally effective amounts of a supplement selected from the group consisting of vitamin A. D and E. sacorbic acid, biotin, panthothenic, choltine, niacin, pyridoxine, riboflavin, thiamine, calcium, phosphorus, NaCl, copper, tron, manganess, iodine, zinc and combinations thereof.

The animal feed of claim 22 in the form of a paste.
 The animal feed according to claim 23, which is a cat

feed.

25. The animal feed according to claim 23, which is a dog feed.

26. The animal feed according to claim 23, which is a horse feed.

 A therapeutic and Chondroprotective/Restorative composition comprising:

 (a) an effective amount of hyaluronic Acid or its pharmaceutically acceptable salts;

(b) an effective amount of a therapeutic drug; and

(c) optionally a pharmaceutically acceptable carrier. 28. The therapeutic and Chandoprotective/Restorative composition of claim 27 wherein said therapeutic drug is selected from the group consisting of acetaminophen, acetic acid, acetylsalicytic acid, buffered acetylsalicytic acid, albuterol, albuterol sulfate, ethanol isopropanol, albantoin, albo, albumium acetane, alumium carbonale, alumium

chlorohydrate, aluminum hydroxide, alprozolam, amino acids, aminobenzoic acid, amoxicillin, ampicillin, amsacrine, amsalog, anethole, aspariame, atenolol, bacitracin, balsam peru, beclomethasone dipropionate, benzocaine, benzoic acid, benzophenones, benzoyl peroxide, biotin, bisacodyl, bornyl acetate, bromopheniramine maleate, buspirone, caffeine, calamine, calcium, calcium carbonate, calcium casinate, calcium hydroxide, camphor, captopril, cascara sagrada, castor oil, Cephalosporins, cefacior, cefadroxil, cephalexin, cetylalcohol, cetylpyridinium chloride, chelated minerals, chloramphenicol, chlorcyclizine hydrochloride, chlorhexidine gluconate, chloroxylenol, chloropentostatin, chlorpheniramine cholestyramine resin, choline bitartrate, cimetidine hydrochloride, cinnamedrine hydrochloride, citalopram, citric acid, Clenbuterol, cocoa butter, cod liver oil, codeine and codeine phosphate, clonidine, clonidine hydrochloride, clorfibrate, ciprofloxacin HCl, cyanocobalamin, cyclizine hydrochloride, DMSO, danthron, Dantrium, dexamethazone, dexbrompheniramme maleate, dextromethorphan hydrobromide, diazapam, dibucaine, dictofenac sodium, digoxin, diltiazem, dimethicone, dioxybenzone, diphenhydramine citrate, diphenhydramine hydrochloride, docusate calicum, docusate potassium, docusate sodium, doxycycline hyclate, doxylamine succinate, efaroxan, enalapril, enoxacin, erythromycin, estropipate, ethinyl estradiol, ephedrine, eninephrine bitartrate, erythropoietin, eucalyptol, ferrous fumurate, ferrous gluconate, ferrous sulfate, folic acid, fosphenytoin, Flunixin Meglumine, fluoxetine HCl, furosemide, gabapentan, gentamicin, Gentocin sulfate, gemfibrozil, glipizide, glycerin, glyceryl stearate, griscofulvin, guaifenesin, hexylresorcinol, hydrochlorothiaxide, hydrocodone bitartrate, hydrocortisone, hydrocortisone acetate, 8-hydroxyquinoline sulfate, ibuprofen, indomethacin, inositol, insulin, iodine, ipecae, iron, isoxicam, Isoxuprine, ketamine, Ketofin, koalin, lactic acid, lanolin, lecithin, lidocaine, lidocaine hydrochloride, lifinopril, liotrix, lovastatin, MSM (methylsullonylmuthane), magnesium carbonate, magnesium hydroxide, magnesium salicylate, magnesium trisilocate, mefenamic acid, meclofenanic acid, meclofenamate sodium, medroxyprogesterone acetate, methenamine, mandelate, Methocarbamol, menthol, meperidine hydrochloride, metaproterenol sulfate, methyl nicotinate, methyl salicylate, methylcellulose, methsuximide, metromidazole, metromidazole hydrochloride, metoprolol tartrate, miconazole nitrate, mineral oil, minoxidil, morphine, naproxen, naproxen sodium, nifedipine, neomycin sulfate, Neomycin-Bacitracin, niacin, niacinamide, nicotine, nicotinamide, nitroglycerin, nonoxynol-9, norethindone, porethindone acetate, pystatin, octoxynol, octyl dimethyl PABA, octyl methoxycinnamate, omega-3 polyunsaturated fatty acids, omeprazole, oxolinic acid, oxybenzone, oxtriphylline, para-aminobenzoic acid (PABA), padimate O, paramethedione, Penicillin, pentastatin, peppermint oil, pentaerythriol tetranitrate, pentobarbital sodium, pheniramine maleate, phenobarbital, phenol, phenolphthalein, phenybutazone, phenylephrine hydrochloride, phenylpropanolamine, phenylpropanolamine hydrochloride, phenyloin, phenelzine sulfate, pirmenol, piroxicam, polymycin B sulfate, notassium chloride, potassium nitrate, prazepam, prednisone, prednisolone, procainamide hydrochloride, procaterol, propoxyphene, propoxyphene HCl, propoxyphene napsylate, pramiracetin, pramoxine, pramoxine hydrochioride, propronolal HCl, pseudoephedrine hydrochloride, pseudoephedrine sulfate, pyridoxine, quinapril, quinidine gluconate, quinestrol, ralitoline, ranitadine, resorcinol, ribuflavin, salicylic acid, sesame oil, shark liver oil, simethicone, sodium bicarbonate, sodium citrate, sodium fluoride, sodium monofluorophosphate, Sulfa-drugs, sulfanethoxazole, sulfur, tacrine, tacrine HCl, theophylline, terfenidine, thioperidone, trimetrexate, triazolam, timolol maleate, tretinoin, tetracycline hydrochloride, tolmetin, tolnaftate, triamcinolone, triclosan, triprolidine hydrochloride, undecylenic scid, vancomycin, verapamil HCl, vidaribine phosphate, vitamin A, vitamin B, vitamin C, vitamin D, vitamin E, vitamin K, witch hazel, xylometazoline hydrochloride, zinc, zinc sulfate, and zinc undecylenate,

29. A Chondroprotective/Restorative composition in paste form comprising:

- (a) an effective amount of Hyaluronic Acid or its pharmaceutically acceptable salts; and
- (b) a sufficient amount of molasses to make a paste.

 30. The Chondroprotective/Restorative composition of
- claim 29 further including glucosamine sulfate.

 31. The Chondroprotective/Restorative composition of claim 30 further including chondroitin sulfate.
- 32. The Chondroprotective/Restorative composition of claim 31 further including nutritionally effective amounts of vitamins and minerals.
- 33. A method of enhancing chondrocyte synthesis in a mammal which method comprises administering orally to said mammal an effective amount of the composition according to claim 31.
- 34. A method for inhibiting onzymes that degrade cartilage, and reduce pain and synovitis in a mammal which method comprises administering orally to said mammal an effective amount of the composition according to claim 31.
- 35. A Chondroprotective/Restorative composition in gel form comprising;
 (a) an effective amount of Hyaluronic Acid or its phar-
 - (b) water; and

maceutically acceptable salts;

- (c) a sufficient amount of carboxymethylcellulose or its sodium salt to make a gel.
- 36. The Chondroprotective/Restorative composition of claim 35 further including glucosamine sulfate.
- The Chondroprotective/Restorative composition of claim 35 further including chondroitin sulfate.
- The Chondroprotective/Restorative composition of claim 35 further including mutritionally effective amounts of vitamins and minerals.

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(12) United States Patent Pierce

(10) Patent No.: US 6,924,273 B2 (45) Date of Patent: Aug. 2, 2005

(54) CHONDROPROTECTIVE/RESTORATIVE COMPOSITIONS AND METHODS OF USE THEREOF

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(57) ABSTRACT

The instant invention provides a method of treating or preventing osterabritis, joint effusion, joint inflammation and pain, synovitis, lameness, post operative arthroscopic surgery, deterioration of proper joint function including joint mobility, the reduction or inhibition of metabolic activity of chondrocytes, the activity of enzymes that degrade cartillage, the reduction or inhibition of the production of Hyaluronic acid, said method comprising orally administering to a mammalian species a therapeutically acceptable saits thereof. Additionally, compositions containing hyaluronic acid, chondroitin sufface, and glucosamine sulfate in a paste formulation are also disclosed which can be administered on their own or can be used as a feed additive.

28 Claims, No Drawings

CHONDROPROTECTIVE/RESTORATIVE COMPOSITIONS AND METHODS OF USE THEREOF

This application claims benefit of application Ser. No. 5 60/237,838 filed Oct. 03, 2000.

FIELD OF INVENTION

The present invention relates to medically useful preparations based on hyaburonic acid and plamaceutically) acceptable salts thereof, a naturally-occurring substance found in animal fissue, and especially in rooster comb, vitreous humour, unabilical cords, and synovial fluid of marmais. This invention also relates to new orally administrable formulations containing hyaburonic acid. The instant is invention is also directed to chondroprotective/restorative compositions containing hyaburonic acid. This invention has related to new pharmaceutical formulations containing hyaburonic acid. This invention is described in the property of the property of

The present invention is also directed to veterinary formulations containing hyaluronic acid and additional bioeffective active ingredients such as bioactive agents useful in the treatment of domesticated animals especially horses. This invention also provides methods for treating horses in need of chondroprotection. The invention is further directed to pharmaceutical compositions containing hyaluronic acid, glucosamine and chondroitin. The present invention also relates to a method of treating aseptic synovitis in horses with hysteronic acid atone or in combination with other active ingredients. More specifically, the present invention is also intended for therapeutic treatments of arthritis and related conditions using pharmaceutical compositions containing hyaluronic acid as well as other active ingredients effective in the treatment of joint diseases. The compositions of the invention are particularly useful in the veterinary field but are also very useful in treatment of humans.

This invention further relates to the oral summistration of florms of hyalmonic acid and pharmacousically acceptable salts thereof such as sodium hyaluronate, and orally administrated desage forms containing forms of hyalmonic acid, for the prevention and/or treatment of diseases such as accountritis, joint effusion, joint inflammation and pain, asynovitis, and many other diseases associated with cartilage degeneration.

The instant invention also provides gels of hyaluronic acid with carboxymethylcellulose.

BACKGROUND OF THE INVENTION

Hybulronic acid (HA) exists as a naturally-occurring polysaccharide (also known as a mucoid polysaccharide) take to navola polysaccharide (also known as a mucoid polysaccharide) that can be extracted from such diverse sources as rooster 55 comb, umbilical ecod, vitrous humos, sprovial fluid, pathologic joints, skin and group A and C hemolytic Streptococci. The hyduronic acid is also defined as a high viscosity naturally occurring glycosaminoglycan having a polymeric structure containing alternating Nacetyl-D-glucosamine and D-glucorronic acid monosaccharide units linked with β 1–14 bonds and the disaccharide units linked with β 1–3 glycoxide bonds. It occurs usually as the sodium salt and has a molecular weight range of about 50,000 to 8x.100 Paltons.

Hyaluronic acid is a naturally occurring glycosaminoglycan. HA is ubiquitous in the organism, with the highest concentration found in soft connective tissue and joint fluid.

It is a constituent of the intercellular matrix of connective tissue that exists in almost all verderstas. It plays an important role in a number of physiological functions, including protection and labrication of cells, maintenance of the structural integrity of tissues, transport of molecules and cells, cell migration, cell function and differentiation, and fluid retention and regulation. The clinical benefits of intraarticular HA in the borse are well published.

Natural Hyaluronic seed is polydisperse in respect of molecular weight and is known to show excellent biscompatibility even when implanted or injected into the body by virtue of the absence of species and organ specificity. However, because of the relatively short in vivo residence time of Hyaluronic acid solution in biological applications, improvements in the persistency of Hyaluronic acid by chemical crosslinking with various chemical modifiers has been attempted to broaden its use for medical materials.

The isolation and characterization of Hyahronic acid is described in Meyer et al. J. Biol. Chem. 107, 629 (1934); J. Biol. Chem. 114, 689 (1936); Balazs, Fed. Proc. 17, 1086 (1938); Laurent et al; Biochim. Biophys. Acta 42, 476 (1960). The structure of Hyahronic acid was elucidated by Weissman et al. J. Am. Chem. Soc. 76, 1753 (1954) and Meyer, Fed. Proc. 17, 1075 (1958).

Hyaluronic acid is an important component of the intercellular matrix. Specifically, the highest levels are found in the eye and synovial fluid of joints. In joints, its primary role is that of lubrication, reducing pain, and inflammation. In arthritic joints HA is deficient. In healthy joints, synovial fluid supplies nutrition to the articular cartilage and has incomparable functions as a lubricant and as a shock absorber. It has been determined that its excellent viscoelastisity owes heavily to one of the main components, present therein, Hvaluronic acid. Concentration and molecular weight analyses of Hyaluronic acid demonstrated the concentration and molecular weight of Hyaluronic acid in the synovial fluid from patients with arthritis such as osteoarthritis and chronic articular rheumatism generally tended to be lower than in normal synovial fluid, and the lower concentration and molecular weight of Hysluronic acid were closely associated with development of locomotor dysfunction and pain attributable to the weaker lubricating action and the weaker protecting action on the surface of the articular cartilage of synovial fluid.

Degradation of the structures in articular cartilage is a typical characteristic of all diseases resulting in chronic destruction of the joint structures. Examples of such disorders are rheumatoid arthritis, psoriatic arthritis, and osteoarthrosis. Also, acute inflammation of a joint is often accompanied by destruction of the cartilage, although in most cases this will not develop into the chronically destructive disease. It is not known which factors are crucial for the acutely inflamed joint to either proceed to healing or develon into the chronic process. Examples of diseases involving acute ioint inflammation are versinia arthritis, pyrophosphate arthritis, gout arthritis (arthritis urica), septic arthritis and various forms of arthritis of traumatic etiology. Among other factors potentially conducive to the destruction of articular cartilage may be mentioned, for instance, treatment with cortisone; this has been known for a long time to accelerate the degenerative process in osteoarthrosis.

Such a so-called "steroid arthropathy" occurs far too often as an undestrable side effect of intra-articular corrisone treatment and can be avoided only by providing for a sufficiently long period of rest after the treatment. Steroid arthropathy is characterized by an advanced degree of articular destruction and X-ray-detectable changes of the same type as occur in advanced degenerative articular disease (Nizolek, D H & White, K K, Cornell Vet. 1981, 71:355-75). According to what is at present accepted as an explanation of the degenerative arthropathy development 5 following treatment with cortisone, this arthropathy is believed to be caused by a primary effect on the chondrocyte metabolism. It should be noted, however, that the actual conditions prevailing in cases of arthritis with severe inflammation of the joint are of a rather more complex character, 10 since in those cases injection of cortisone appears to have an overall positive effect on the clinical picture.

Also, it is well known that articular cartilage is composed of about 70% of water, chondrocytes and a cartilage matrix. The major components constituting the articular matrix are 15 collagen and proteoglycan; the proteoglycan having good water retention characteristics is contained in the network of collagen having a reticulated structure. The articular matrix is rich in viscoelasticity and has an important role in reducing the stimulus and load imposed on the cartilage in 20 order to maintain the normal morphology and function of the articular cartilage.

Osteoarthritis and rheumatoid arthritis are representative of the diseases accompanied by the destruction of the cartilage matrix. It is thought that the destruction of the 25 matrix in these diseases is triggered by mechanical stresses with aging in the case of osteoarthritis and by excess proliferation of the surface layer cells of the synovial membrane, pannus formation and inflammatory cell infiltration in the case of rheumatoid arthritis, and both phenomena are caused through the induction of proteases. Since the degradation of articular cartilage is progressed in the extracellular region at a neutral pH, it is said that a matrix metalloprotease (hereinafter referred to as "MMP" or "MMPs" when used as the general term) whose optimal pH 35 is in the neutral range plays a leading role in the degradation.

No medical cure exists for osteoarthritis. The progressive degeneration of the joint due to ostcoarthritis is irreversible. Present therapies are directed to palliative medical therapies to reduce inflammation and pain and surgical therapies to reconstruct an affected joint or, in severe cases, to replace the joint with an artificial, prosthetic joint.

Injection of high molecular weight Hyaluronic acid solution into diseased joints has been widely adopted as an 45 effective measure for ostcoarthritis among those articular diseases, and the source of high purity HA preparations for this purpose is cockscombs. Such HA preparations from cockscombs are biologically inherent and quite safe but usually have to be administered as frequently as several to 50 10 times to show significant therapeutic effect. Persistency tests on rabbits revealed that HA with a molecular weight of less than 1000000 administered into the knee joint cavities disappeared from the knee joint cavities in 1 to 3 days and suggested the need of frequent administrations (Blood 55 Coagulation and Fibrinolysis, vol. 2(1): 173-8, (1991)).

On the other hand, the molecular weight of HA found in the living body is reported to be as high as millions to 10000000, and a crosslinked HA derivative obtained by treatment with a chemical crosslinker has been developed as 60 centically acceptable carrier. a therapeutic agent for knee joints with the idea that high molecular weight HA closer to the biologically intact one is likely to have higher effect. Reportedly, the crosslinked HA persisted for a period as long as 20 to 30 days after administration into rabbit knee joint cavities in the above- 65 mentioned persistency tests and produced sufficient effect when administered three times in chinical tests, and is

practically used as a therapeutic agent for arthritis (see Blood Coagulation and Fibrinolysis, ibid.; and Journal of Rheumatology vol. 25(9): 1813-9 (1998)).

A need exists for an effective palliative medication for the treatment of asteoarthritis and other joint diseases which is both safe and effective when used for both short-term and long-term therapy and which can be administered orally.

OBJECTS OF THE INVENTION

It is a first object of the present invention to provide a method for treating mammals having joint diseases by oral administration of hyaluronic acid and salts thereof.

It is another object of the instant invention to provide novel chondroprotective/restorative compositions.

A further object of the invention is to provide a novel chondroprotective/restorative composition containing hyaluronic acid in paste or gel form.

A still further object of the invention is to provide novel chondroprotective/restorative compositions containing hyaluronic acid, glucosamine sulfate and chondroitin sulfate

An additional object of the invention is to provide chondroprotective/restorative compositions containing hyaluronic acid and bioeffective materials.

A still additional object of the invention is to provide chondroprotective/restorative compositions containing hyaluronic acid, vitamins and minerals.

An additional object of the present invention is provide chondroprotective/restorative compositions containing hyaluronic acid, vitamins and minerals.

Another main object of the present invention is to provide an aqueous gel containing hyaluronic acid and molasses.

Another object of the present invention is to provide paste formulations containing hyaluronic acid, glucosamine sulfate and molasses.

An additional object of the invention is to provide gel formulations containing HA in a carboxymethylcellulose

A further object of the invention is to provide animal feeds containing hyaluronic acid.

These and other objects of the invention will become apparent from the description hereinafter.

SUMMARY OF THE INVENTION

The present invention provides a method for treating or preventing esteoarthritis, joint effusion, joint inflammation and pain, synovitis, lameness, post operative arthroscopic surgery, deterioration of proper joint function, the reduction or inhibition of metabolic activity of chondrocytes, the activity of enzymes that degrade cartilage, the reduction or inhibition of the production of hyaluronic acid, said method comprising orally administering to a mammalian species a therapeutically effective amount of hyaluronic acid or pharmaceutically acceptable salts thereof.

The invention is also directed to a Chondroprotective/ Restorative composition comprising Hyaluronic Acid or its pharmaceutically acceptable salts and optionally a pharma-

The instant invention also provides a Chondroprotective/ Restorative composition comprising: (a) an effective amount of Glucosamine sulfate; (b) an effective amount Hyaluronic Acid or pharmaceutically acceptable salts thereof; and (c) optionally a pharmaceutically acceptable carrier.

Additionally, the invention provides a Chondroprotective/ Restorative composition comprising: (b) an effective

amount of Chondroitin sulfate; (b) an effective amount of Hyaluronic Acid or pharmaceutically acceptable salts thereof; and (c) optionally a pharmaceutically acceptable

The instant invention further provides a 5 Chondroprotective/Restorative composition comprising: (a) an effective amount of Glucosamine sulfate; (b) an effective amount of Chondroitin sulfate; (c) an effective amount of Hyaluronic Acid or pharmaceutically acceptable salts

The Chondroprotective/Restorative compositions of the invention further include nutritionally effective amounts of a supplement selected from the group consisting of vitamin A, D and E, ascorbic acid, biotin, panthothenic, choline, 15 niacin, pyridoxine, riboflavin, thiamine, calcium, phosphorus, NaCl, copper, iron, manganese, iodine, zinc and combinations thereof.

The invention is also directed to an animal feed having Chondroprotective/Restorative benefits comprising: (a) a nutritionally effective feed base selected from the group consisting of grains, proteins and fats; and (b) an effective amount of Hyaluronic Acid or pharmaceutically acceptable salts thereof.

Furthermore, the invention relates to a therapeutic Chondroprotective/Restorative composition comprising: (a) Hyaluronic Acid or its pharmaceutically acceptable salts; (b) a therapeutic drug; and (c) optionally a pharmaceutically acceptable carrier.

The invention is also directed to a Chondroprotective/ Restorative composition in paste form comprising: (a) an effective amount of Hyaiuronic Acid or its pharmaceutically acceptable salts; and (b) a sufficient amount of molasses to make a paste.

Additionally, the invention also relates to a Chondroprotective/Restorative composition in gel form comprising; (a) an effective amount of Hyaluronic Acid or its pharmaceutically acceptable salts; and (b) a sufficient amount of carboxymethylcellulose to make a paste.

DETAILED DESCRIPTION OF INVENTION

In the first preferred embodiment of the invention, there is provided viscosupplementation of joints by oral administration of sodium hyaluronate (HA) to mammals and more 4 in particular to racing thoroughbreds. Applicant's conducted a double blind placebo-controlled study wherein ten horses were randomly chosen and given an oral gel (also known as Conquer and containing 100 mg of hyaluronic acid) for 59 days. Every parameter used to measure soundness was a improved in the HA treated group. Also, every parameter used to measure routine maintenance of the racing Thoroughbred was improved in the HA treated group. All horses in the treated group with pre-existing conditions showed clinical improvement during the study.

In conducting our study, ten actively training Thoroughbreds were randomly selected. Five were given a placebo gel and five were given a gel containing 100 mg of Sodium Hyaluronate. The duration of the study was 59 days. The ages of the horses varied: one two-year old, five three-year olds, two four-year olds, and two five-year olds. Because the half-life of circulating HA is two days or less, the horses were given 100 mg once daily. Upon completion of the study, training and veterinary records were evaluated. Number of days to the track was compared to number of days walked. In addition, horses receiving NSAIDS during the study for any reason were recorded as were horses examined

for any lameness. Horses were evaluated weekly for joint effusion, pain on flexion, and signs of lameness. Horses radiographed due to lameness were recorded. Horses with pre-existing conditions were monitored and periodically evaluated

The results of oral administration of HA are listed in Tables 1 and 2 below. Treated horses went to the track more days than the non-treated group (40 versus 32). Horse 110, thereof, and (d) optionally a pharmaceutically acceptable 10 of the non-treated group sustained a cortical stress fracture 33 days into the study. With this non-articular injury removed from the study, the average days to the track of the non-treated group changes from 32 to 35 days. All of the non-treated horses were examined for lameness at some time during the study. None of the treated horses were examined for lameness. All horses in the treated group with preexisting conditions improved. NSAIDS, primarily phenylbutazone, was used at some time during the study in 5 of 5 of the non-treated horses. Less was used in the treated group, 2 of 5. None of the treated group were radiographed during the study while 3 of 5 of the non-treated group had radiographs taken. More horses developed new signs of synovial effusion in the non-treated group, 3 of 5, than in the treated group, 1 of 5. The treated group required less bandaging (3 of 5) than the non-treated group (5 of 5).

| Horses | Ags | Sex | Days To Track | Days Walked | Examined For Lameness | NSAIDS | Radio- graphed |
|--------|-----|-----|---------------------|----------------|-----------------------------|--------|-------------------|
| | | | TRE | ATED H | ORSES | | |
| 101 | 5 | G | 4.5 | 14 | NO | YES | NO |
| 102 | 2 | F | 41 | 18 | NO | NO | NO |
| 105 | 4 | M | 38 | 21 | NO | NO | NO |
| 106 | 5 | M | 31 | 28 | NO | NO | NO |
| 109 | 4 | M | 45 | 13 | NO | YES | NO |
| | | | TRE | ATED TO | TALS | | |
| N/A | N/A | N/A | 201 | 94 | NONE | 2/5 | NONE |
| | | | (Avo. | (Ave. | | | |
| | | | 40) | 19) | | | |
| | | | NON-T | REATED | HORSES | | |
| 103 | 3 | C | 44 | 15 | YES | YES | NO |
| 104 | 3 | С | 19 | 40 | YES | YES | YES |
| 197 | 3 | £ | 4.3 | 16 | YES | YES | NO |
| 168 | 3 | C | 34 | 25 | YES | YES | YES |
| 210* | 3 | Ç | 19 | 40 | YES | YES | YES |
| | | _ | NON-T | REATED | TOTALS | | |
| N/A | N/A | N/A | 159 | 136 | 5/5 | 5/5 | 3/5 |
| | | | (Avc. | (Ave. | | | |
| | | | 32) | 27) | | | |

*Horse 110 sustained a cortical stress fracture 33 days into the study. By removing him from the totals the average days to the track becomes 35 days instead of 32 days.

TARLE 2

| 60 | Horse | Pre- existing Condition | Condition | Improved | New Joint Effusion During Study | Location |
|----|-------|-------------------------------|------------------------|------------|--|---------------|
| | | | TREATED | HORSES | | |
| | 101 | YES | Osslets | YES | NO | N/A |
| 65 | 102 | NO YES | N/A Severe T Sheath | N/A YES | YES NO | CARPUS N/A |
| | 2110 | 163 | DE CHICAGO | 340 | | 1411 |

TABLE 2-continued

| Horse | Pre- existing Condition | Condition | Improved | New Joint Effusion During Study | Location |
|-------|-------------------------------|------------------------|-----------|--|----------|
| 106 | YES | Chronic Ossists | YES | NO | N/A |
| 109 | YES | Osslets | YES | NO | N/A |
| | | NON-TREAT | ED HORSES | | |
| 103 | YES | Stiffnoss Behind | YES | YES | Carpus |
| 104 | NO | N/A | N/A | NO | N/A |
| 107 | NO | N/A | N/A | YES | Petlocks |
| 108 | YES | Left Front Soreness | NO | YES | Stifles |
| 119 | NO | N/A | NVA | NO | N/A |

As can be appreciated from Tables 1 and 2, horses maintained on a daily dose of oral sodium hyaluronate showed improvement of all soundness characteristics mea- 20 sured. Horses with pre-existing synovitis improved while on oral HA. Accordingly, the data suggests that Oral sodium hyaluronate appears to be effective in preventing lameness in the racing Thoroughbred. None of the horses in the treated group were examined for lameness while in the non-treated 25 group, two horses developed mild forelimb lameness which were subtle and difficult to diagnose with diagnostic nerve blocks, one horse became painful in his back and front feet and a fourth horse became acutely lame after a race. This lameness could not be completely diagnosed with nerve 30 blocks therefore a bone scan was performed. Results showed increased uptake in the left carpus, left front fetlock, and solar margins of the foot. After resting about 30 days, this horse resumed training. The present invention provides evidence of HA's ability to have a performance enhancing 35 effect in the racing Thoroughbred when used orally. In addition, oral administration of HA is effective in the treatment of synovitis associated with osteoarthritis

In the second preferred embodiment of the invention, an oral preparation containing sodium hydronate was evaluated in the treatment of aseptic synovits. Horses chosen had clinical signs of joint disease and were treated with 100 mg of Sodium Hyaluronate, 1 g Chondroitin sulfate, and 200 mg Vitamin C for 30 days.

In conducting the above study, six adult horses were administered 100 mg of sociation Mayalmonate, 1 g of Chondrolim sulfate, and 200 mg Vitamin C daily in an oral preparation. The horses were treated for 30 days and were monitored continuously. Clinical evaluations were per-gofferned on day 1, day 30, and at day 45 (tow weeks after discontinuation of treatment). Clinically, four horses had significant aspectic soyotis of the metacapophalangeal joints. One horse suffered from villinodular synovitis and one horse had degenerative joint disease of the proximal 50 interphalangeal joint (nighone). The results of the study are summarized in Table 3 below.

TABLE 3

| Symptom | Day 1 | Uny 30 | Day 45 |
|--|--|--|--|
| Oversill evaluation Swelling affusion | inflammed effusion Pain on flexion 6 of 5 horses | Improved in 5 of 6 homes Improved in 5 of 6 homes | Improved in 5 of 6 horses Improved in 5 of 6 horses |
| Joint Pain | 6 of 6 horses | Improved in 5 of 6 borses | Improved in 5 of 6 horses |

TABLE 3-continued

| Symptom | Day 1 | Day 30 | Day 45 |
|--------------------|---------------------------------------|------------------------------|------------------------------|
| Lameness | Grade 1 or 2 lame in 6 of 6 horses | Sound in 5 of 6 horses | Sound in 5 of 6 horses |
| Range of Motion | Decreased in 6 of 6 houses | Improved in 5 of 6 horses | Improved in 5 of 6 horses |

As can be appreciated from Table 3, significant improvement was seen in five of six horses. The amount of synovial effusion and inflammation decreased in all but one case. There was improvement of lameness and decreased pain on Resion. The horse diagnosed with degenerative joint disease of the proximal interplalangeal joint showed no improvement. Oral delivery of sodium hyslutonate is a viable alternative for treatment of synovitis in the horse. It is very safe with no side offects being reported in this study.

In a third embodiment of the invention, another oral gel consisting of 100 mg per dose of sodium hyaluronate was evaluated. Horses chosen had significant signs of synovitis and joint pain. Treatment was continued for 21 days. In conducting the study, four wearling Thoroughbred toals and one three year old Thoroughbred racehorse were given 100 mg daily of sodium hyaluronate in a gel formulation. All horses were diagnosed with moderate to severe synovitis of the metacarpolphalangeal joints. Two of the foals and the three year old raceborse had moderate to severe effusion and pain in both fore fetlocks while the other two had marked synovitis of all four fetlocks. Three of the foals were Grade 1/5 lame and one foal was grade 2/5 lame at a walk and trot. The race horse was not lame at a walk or trot but was painful on flexion. All foals were very painful on flexion and lameness was significantly worsened following fetlock flexion tests. Radiographs of the affected fetlocks did not reveal any bony abnormalities. Treatment was continued for 21 days and all horses wee evaluated weekly. No other treatments were administered during this time.

The results are summarized in Table 4. In one foal with effusion in all four fetlocks (Grade 1/5 lame), significant improvement was seen after seven days of treatment. Synovial effusion had decreased and the foal was sound at a walk and trot. Slight lameness was observed after fetlock flexion. By week two, this foal's joints were considered normal and no pain on flexion or lameness could be detected. In the second foal with marked effusion in all four fetlocks (Grade 2/5 lame), moderate synovial effusion was still present at seven days. After fetlock flexion, this foal's lameness worsened to a Grade 4/5. At the 14th day exam, significant improvement was observed. The amount of joint swelling had decreased dramatically and the foal's lameness was improved. There was lameness pain on flexion and the lameness after fetlock flexion improved to a Grade 1/5. At the 21st day exam, the joints were considered normal and the foal was sound at a walk and trot. The third and fourth foals with synovial effusion in the front fetlocks showed significant improvement in seven days. They continued to have so slight pain on flexion and slightly lame after fetlock flexion. By 14 days these foals had slight effusion but were sound and negative to fetlock flexion. At the 21" day exam they were considered normal. The 3 year old racehorse had a significant decrease in synovitis at day 7. By the 14th day 65 there was slight effusion and no pain on flexion. At 21 days, there continued to be slight effusion but no lameness or pain on flexion.

| Horse | Day 1 | Day 7 | Day 14 | Day 21 |
|-------|---|--|---------------------------------------|-------------------------|
| ė1 | Moderate effusion in all four | Mild effusion is all four | No effusion, Sound/ | No effusion. Sound/No |
| | fetlocks. Grade 1/5 lame/ Moderate pain on flexion | feflock/Sound/Slight pain on flexion | No pain on flexion | pain on flexion |
| #2 | Severe effusion in all four | Moderate effusion in all | Mild offusion in front | Slight offusion in from |
| | Petlocks Grade 2/S Jame. | four fetlocks, Grade 1/5 | Grade 1/5 lame | fetlocks, Sound, Stight |
| | Severa pain on flexion | lame ferlocks. Moderate exis on flexion | Moderate pain on Sexion | pain on flexion |
| #3 | Mogernie effusion on front | Mild effusion in front | Slight effusion in front | No effusion, Sound |
| | Fetlocks. Grade 1/5 lame, Mild pain on flexion | Petiocks, Sound, Mild pain on Sexion | Petlock Sound, No pain on fiscion | No pain on flexion |
| #4 | Moderate effusion on front | Mild offusion is front | Slight effusion in front | No effusion, Sound |
| | Fetlocks, Grade 3/5 lame, | Petiocks. Sound, Mild pain | Fetlock, Sound, No. | No pain on flexion |
| | Mild pain on flexion | on fickion | pain on flexion | |
| 85* | Moderate effusion in front | Mild effusion in front | Slight effusion in front | |
| | Feticeks. No Lameness, Mild pain on flexion | Fetlocks. Sound, slight pain on flexion | Petiock. Sound, No pain on flexion | No pain on flexion |

[&]quot;Three year old racehorse

In a further clinical trial of the invention, 24 hockey players were treated via oral administration with a combination of sodium hyaluronate and chondroitin sulphate in gel form as exemplified in Example 16 for three months. The dosage levels were 0.1-0.5 mg/Kg of body weight. Agreater 25 than sixty five percent improvement in their knee joint was observed.

Additionally, 27 human patients were treated via oral administration with a combination of sodium hyaluronate Example 16 for three months after knee surgery. The dosage levels were 0.1-0.5 mg/Kg of body weight. At least a 58% improvement was observed on their knee joints.

It should be noted that in treating mammals the recommg/Kg of body weight. Accordingly, for a human the dosage ranges can be from 7 to 40 mg; while for a horse the range can be from 50-250 mg and for a dog the ranges would be 2-8 mg.

In a fourth embodiment, the invention also provides 40 chondroprotective and restorative compositions which are very useful for oral administration. The compositions contain 10 to 2000 mg of hyaturonic acid and optionally a pharmaceutically acceptable carrier.

In a fifth embodiment, the present invention relates to 45 chondroprotective and restorative compositions useful for oral administration containing; (a) 0.01-10 wt % hyaluronic acid or its pharmaceutical acceptable salts; (b) optionally 20-60 wt % glucosamine or its pharmaceutically acceptable salts; (c) optionally 1-15 wt % chondroitin or its pharma- 50 ceutical acceptable saits; (d) optionally nutritionally effective (recommended daily allowance) amounts of a supplement selected from the group consisting of vitamin A, D and E, ascorbic acid, B complex, B12, B1, biotin, panthothenic, choline, niacin, pyridoxine, riboflavin, thiamine, calcium. 55 phosphorus, NaCl, copper, iron, manganese, iodine, zinc and combinations thereof; (e) optionally effective amounts of a bioactive agent or drug; and (f) optionally a pharmaceutically or nutritionally acceptable carrier.

The pharmaceutical acceptable salts of hyaluronic acid 60 include the alkali metal salts as well as the alkaline earth metal salts. Typical salts include sodium hyaluronate, potassium hyaluronate, magnesium hyaluronate and calcium hyaluronate. The preferred salt in the compositions of the invention is sodium byaluronate.

The pharmaceutically effective salts of glucosamine are selected from the group consisting of glucosamine chloride,

glucosamine bromide, glucosamine iodide and glucosamine sulfate. Similarly, with chondroitin the same type of salts are usable i.e., chondroitin chloride, chondroitin bromide, chondroitin sulfate and chondroitin iodide.

The bio-effective or drug component of the invention is selected from the group consisting of angiotensin converting enzyme inhibitors, anti-asthmatics, anti-cholesterolemics, anti-convulsants, anti-depressants, anti-diarrhea preparations, anti-infectives, anti-inflammatory agents, antiand chondroitin sulphate in gel form as exemplified in 30 nauscants, anti-stroke agents, anti-tumor drugs, antitussives, anti-uricemic drugs, amino-acid preparations, antiemetics, antiobesity drugs, antiparasities, antipyretics, appetite stimulants, cerebral dilators, chelating agents, cholecystokinin antagonists, cognition activators, mended daily dosage for hyaluronic acid is about 0.1 to 0.5 35 deodorants, dermatological agents, diabetes agents, diuretics, erythropoietic drugs, fertility agents, synthetic hormones, laxatives, mineral supplements, neuroleptics, neuromuscular agents, peripheral vaso-dilators, prostaglandins, vaginal preparations, vaso-constrictors and vertigo agents.

The bio-effecting agent is selected from the group consisting of acetaminophen, acetic acid, acetylsalicylic acid, buffered acetylsalicylic acid, albuterol, albuterol sulfate, ethanol isopropanol, allantoin, aloe, aluminum acetate, aluminum carbonate, aluminum chlorohydrate, aluminum hydroxide, alprozolam, amino acids, aminobenzoic acid, amoxicillin, ampicillin, amsacrine, amsalog, anethole, aspariame, atenolol, bacitracin, balsam peru, beclomethasome dipropionate, benzocaine, benzoic acid, benzophenones, benzoyl peroxide, biotin, bisacodyl, bornyl acetate, bromopheniramine maleate, buspirone, caffeine, calamine, calcium, calcium carbonate, calcium casinate, calcium hydroxide, camphor, captopril, cascara sagrada, castor oil. Cephalosporins, cefaclor, cefadroxil, cephalexin, cetylalcohol, cetylpyridinium chloride, chelated minerals, chloramphenicol, chlorcyclizine hydrochloride, chlorhexidine gluconate, chloroxylenol, chloropentostatin, chlorpheniramine maleate, cholestyramine resin, choline bitartrate, cimetidine hydrochloride, einnamedrine hydrochloride, citalogram, citric acid, Clenbuterol, cocoa butter, cod liver oil, codeine and codeine phosphate, clonidine, clonidine hydrochloride, clorfibrate, ciprofloxacia HCl, evanocobalamin, evelizine hydrochloride, DMSO, danthron, Dantrium, dexamethazone, dexbrompheniranime maleate, dextromethorphan hydrobromide, diazapam, dibucaine, diclofenac sodium, digoxin, dilliazom, dimethicone, dioxybenzone, diphenbydramine citrate, erythromycin, estropipate, ethinyl estradiol, ephedrine, epinephrine bitartrate, erythropoietin, eucalyptol, ferrous 5 fumarate, ferrous gluconate, ferrous sulfate, folic acid, fosphenytoin, Flunixin Meglumine, fluoxetine HCl. furosemide, gabapentan, gentamicin, Gentocin sulfate, gemfibrozil, glipizide, glycerin, glyceryl stearate, hydrochlorothiaxide, hydrocodone bitartrate, hydrocortisone, hydrocortisone acetate, 8-hydroxyquinoline sulfate, ibuprofen, indomethacin, inositol, insulin, iodine, ipecac, iron, isoxicam, ketamine, Ketofin, koalin, lactic acid, lanolin, lecithin, lidocaine, lidocaine hydrochloride, 15 lifinopril. liotrix, lovastatin, (methylsulfonylmethane), magnesium carbonate, magnesium hydroxide, magnesium salicylate, magnesium trisilocate, mefenamic acid, meclofenanic acid, meclofeme mandelate. Methocarbamol, menthol, meperidine hydrochloride, metaproterenol sulfate, methyl nicotinate, methyl salicylate, methylcellulose, methsuximide, metromidazole, metromidazole hydrochloride, metoprolol tartrate, miconazole nitrate, mineral oil, minoxidil, 25 morphine, naproxen, naproxen sodium, nifedipine, neomycin sulfate, Neomycin-Bacitracia, niacia, niacinamide, nicotine, nicotinamide, nitroglycerin, nonoxynol-9, norethindone, norethindone acetate, nystatin, octoxynol, polyunsaturated fatty acids, omeprazole, oxolinic acid, oxybenzone, oxtriphylline, para-aminobenzoic acid (PABA), padimate 0, paramethadione, Penicillin, pentastatin, peppermint oil, pentaerythriol tetranitrate, penphenol, phenolphthalein, phenylbutazone, phenylephrine hydrochloride, phenylpropanolamine, phenylpropanolamine hydrochloride, phenytoin, phenelzine sulfate, pirmenol, piroxicam, polymycin B sulfate, potassium chloride, potassium nitrate, prazepam, prednisone, prednisolone, procaina- 40 mide hydrochloride, procaterol, propoxyphene, propoxyphene HCl, propoxyphene napsylate, pramiracetin, pramoxine, pramoxine hydrochloride, propronolol HCl, pseudoephedrine hydrochloride, pseudoephedrine sulfate, ralitoline, ranitadine, resorcinol, riboflaviu, salicylic acid, sesame oil, shark liver oil, simethicone, sodium bicarbonate, sodium citrate, sodium fluoride, sodium monofluorophosphate, Sulfa-drugs, sulfanethoxazole, sulfur, tacrine, tacrine HCl, theophylline, terfenidine, 50 thioperidone, trimetrexate, triazolam, timolol maleate, tretinoin, tetracycline hydrochloride, tolmetin, tolnaftate, triamcinilone, trickosan, triprolidine hydrochloride, undecylenic acid, vancomycin, verapamil HCI, vidaribine phosphate, vitamin A, vitamin B, vitamin C, vitamin D, 55 vitamin B. vitamin K. witch bazel, xylometazoline hydrochloride, zinc, zinc sulfate, and zinc undecylenate.

The compositions of the invention can be made in paste form, gel forms, tablets and capsules. The paste form of the invention contains molasses in an amount effective to form 60

The gel forms of the invention are formed by mixing the actives with water and then adding a gelling agent. The gelling agent is selected from the group consisting of cellulose or a cellulose derivative in an amount of from 0.5 65 to 5 wt. % and said cellulose derivative is selected from the group consisting of hydroxypropyl methyl cellulose,

hydroxymethyl cellulose, methyl cellulose, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, cellulose acctate, ethyl cellulose, methyl hydroxy ethyl cellulose, hydroxy ethyl cellulose, cellulose gum carboxymethylcellulose and

sodium carboxymethylcellulose. In making the compositions of the invention, the active materials will usually be mixed with a carrier, or diluted by a carrier, or enclosed within a carrier which may be in the form of a capsule, sachet, paper or other container. When the griscofulvin, guarfenesin, hexylresorcinol, to carrier serves as a diluent, it may be solid, semi-solid or liquid material which acts as a vehicle, excipient or medium for the active ingredient. Thus, the compositions can be in the form of tablets, pills, powders, lozenges, sachets, cachets, elixirs, suspensions, emulsions, solutions, syrups, aerosols (as a solid or in a liquid medium), ointments containing for example up to 10% by weight of the active compound, soft and hard gelatin capsules, suppositories, sterile injectable solutions and sterile packaged powders.

Some examples of suitable carriers, excipients, and dilunamate sodium, medroxyprogesterone acctate, methenam 20 ents include factose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacis, calcium phosphate, alginates, tragacanth, gelatin, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidone, cellulose, water, syrup, methylcelluse, methyl and propylhydroxybenzoates, tale, magnesium stearate and mineral oil. The formulations can additionally include lubricating agents wetting agents, emulsifying and suspending agents, preserving agents, sweetening agents or flavoring agents. The compositions may be formulated so as to provide rapid, sustained or delayed octyl dimethyl PABA, octyl methoxycinnamate, omega-3 30 release of the active ingredient after administration to the patient by employing procedures well-know in the art.

In a sixth embodiment of the invention, an animal feed is provided having chondroprotective and restorative properties. The animal feed base of the present invention comprises tobarbital sodium, pheniramine maleate, phenobarbital, 35 farinaccous material selected from the group consisting of wheat, wheat flour, wheat meal by-products and com in an amount of 25 to 70% by weight based on the total weight of the feed, further comprising proteinaccous material selected from the group consisting of soybean meal, soy flour, peanut meal, cottonseed meal, safflower seed meal in an amount of from 5 to 40% by weight based on the total weight of the feed, further comprising fibrous material selected from the group consisting of soy hulls, cottonseed hulls, rice hulls in an amount of from about 2 to 35% by weight based on the pyridoxine, quinapril, quinidine gluconate, quinestrol, 45 total weight of the feed, further comprising nutritional supplements selected from the group consisting of vitamin A, D and E, ascorbic acid, biotin, panthothenic, choline, niacin, pyridoxine, riboflavin, thiamine, calcium, phosphorus, NaCl, copper, iron, manganuse, iodine, zinc and combinations thereof, in an amount of from 3 to 4% by weight based on the total weight of the feed, further comprising a vegetable oil coating, said oil selected from the group consisting of soybean oil, corn oil, safflower oil, cottonseed oil, peanut oil, in an amount of from 1 to 15% by weight based on the total weight of the feed.

The above feed base is blended with a paste having the following formulation ranges: (a) 0.01-10 wt % hyaluronic acid or its pharmaceutical acceptable salts; (b) optionally 20-60 wt % glucosamine or its pharmaceutically acceptable salts; (c) optionally 1-15 wt % chondroitin or its pharmacentical acceptable salts; (d) optionally nutritionally effective (recommended daily allowance) amounts of a supplement selected from the group consisting of vitamin A, D and E, ascorbic acid, B complex, B12, B1, biotin, panthothenic, choline, niacin, pyridoxine, riboflaviu, thiamine, calcium, phosphorus, NaCl, copper, iron, manganese, iodine, zinc and combinations thereof; (e) optionally effective amounts of a bioactive agent or drug; and (f) 15-35 wt % molasses. The feed of course is formulated in way to provide optimum nutrition and optimum chondroprotection depending on the specific animal and their current state of health.

The present invention is the most unique 5 chondoprotective/restorative agent available. The molasses flavored oral paste provides a practical, efficient, and effective means of administration orally or top dressing feed. When added to the feed, the molasses base binds to the feed to insure total consumption. When necessary, an easy mea- 10 surable dose can be administered orally. The highly palatable formulation of the invention is the first to combine high levels of Glucosamine sulfate (GS) with Chondroitin sulfate (CS) and Hyaluronic Acid (HA) in an easy to absorb, low molecular weight formula. It has also been shown that liquid 15 or paste forms are more readily absorbed than encapsulated or powder forms. The chondroprotective/restorative agent of the invention enhance chondrocyte synthesis, increase synthesis of hyaluronic acid, inhibit enzymes that degrade down or reverse progression of the disease. The present invention, with its unique combination of GS, CS, and HA is the closest yet to satisfying these criteria.

These three substances are the three connective tissue Connective tissue is comprised mainly of collagen and proteoglycans. Proteoglycans provide the framework for collagen and hold water, enhancing the flexibility and resistance to compression needed to counteract physical stress. Glucosamine is the building block needed as the precursor for all subsequent amino sugar synthesis. The formation of N-acetylglucosamine, chondroitin sulfate, and hyaluronic acid require glucosamine for their synthesis. In fact, glu-

Glucosamine sulfate along with Chondroitin sulfate have become very popular supplements administered in the treatment of degenerative joint disease. Recent studies have questioned whether the combination produces better results than Glucosamine sulfate alone. Also there is much debate 40 over which glucosamine salt is preferred. Embodiments of the present invention utilize Glucosamine sulfate as its source of Glucosamine. Most of the past and present research has been performed on the sulfated form. There is evidence that suggests that a component of the activity of GS 45 and CS is related to the sulfate residues found in these compounds. Sulfur is an essential untrient for the stabilization of the connective tissue matrix. It has been proposed that the sulfate molecules of GS and CS contribute to the theraneutic benefits of the compounds in degenerative joint 50 disease. If this is true, it would suggest that GS, as opposed to N-acetylglucosamine and glucosamine HCI, is the best form of glucosamine supplementation. Recently, it has been shown that high-dose glucosamine may provide rapid symptomatic benefit and in the long term repair of damaged 55 cartilage. The high dose of glucosamine not only promotes synthesis of cartilage proteogycans, but stimulates synovial production of hyaluronic acid. This would explain the anecdotal reports that a high dose of glucosamine is beneficial.

As previously explained, the present invention comprises 60 a highly palatable formulation, which is the first to combine high levels of Glucosamine sulfate (GS) with Chondroitin sulfate (CS) and Hyaluronic Acid (HA) in an easy to absorb, low molecular weight formula.

Glucosamine, which is formed in the body as glu- 65 cosamine 6-phosphate is the most fundamental building block required for the biosynthesis of the classes of com-

pounds such as glucolipids, glycoproteius, glycosamineglycans, hyaluronate, and proteoglycans. Directly or indirectly, glucosamine plays a role in the formation of articular surfaces, tendons, ligaments, synovial fluid, skin, bone, heart valves, blood vessels and mucus secretions of the digestive, respiratory and urinary tracts. Glucosamine sulfate is greater than 90% absorbed and is quickly incorporated into articular cartilage following oral administration

In one study, no LD50 was established for Glucosamine sulfate since even at very high levels (5000 mg/kg orally) there was no mortality in mice and rats. While treatment with GS does not produce the initial dramatic reductions in pain normally associated with NSAIDs, its ability to reduce pain is consistent and progressive throughout the course of it's administration, resulting in a long-term improvement in the condition. Glucosamine is a small molecule and is very soluble in water.

Chondroitin Sulfate achieves benefits much more slowly cartilage, and reduce pain and synovitis. It must also slow 20 than glucosamine. Chondroitin bioavailability following oral administration is around 15%. Because of its lower bioavailability, the time needed to see a clinical response is lenethened. Chondroitin improves joint fluidity by drawing water to the cartilage tissue. When this water is drawn into molecules needed to rebuild and synthesize new tissue. 25 the cartilage, it is accompanied by nutrients which are supplied to the cartilage. Additionally Chondroitin helps fight enzymes that inhibit transportation of nutrients into these tissues as it prevents other enzymes from tearing down cartilage tissue. Furthermore, Chondroitin, like The building blocks for all proteoglycans are amino sugars. 30 Glucosamine, promotes the product of key cartilage components such as proteoglycans and it also prevents abnormal

Hyaluronic acid is one of many glycosaminoglycans of physiological significance. Other are Chondroitin sulfate, cosamine makes up 50% of the hyaturonic acid molecule. 35 Heparin sulfate, and Dermatan sulfate. The HA molecule is very similar to that of Chondroitin sulfate. In numerous studies, the oral absorption of CS, HS and DS have been well documented. The bioavailabilities range from 15-20%. Hyaluronic acid has been shown to be absorbed through skin and reach the dermal lymphatics. Also, high levels of hvaluronan has been detected in the intestinal lymphatics. In addition, studies have been performed to determine the effects of HA secreted in saliva. Others have looked at hyaluronic acid production by oral epithelial cells. According to the present invention, there is a beneficial effect when Glucosamine sulfate, Chondroitin sulfate, and Hyaluronic acid are administered orally. Generally, the oral administration of a gel or paste form composition of HA, GS, and CS has a quicker clinical response than is produced when each component of the composition is given individually. A significant difference is an acute or a rapid relief from joint pain, inflammation and swelling achieved by oral administration of the composition. A dramatic improvement over seven to ten days is achieved with the present embodiment, whereas it usually takes weeks for that effect to occur when GS and CS are administered without HA. Another beneficial embodiment is an oral preparation for oral administration of an effective chondroprotective/restorative amount of HA to, for example, an equine. The administration of the HA composition orally and having a clinical effect eliminates more invasive procedures. Other ways to give HA would be more invasive, such an injection by IV or other administration into the joints. Thus, the embodiments of the present invention include oral preparations that are administrable by less invasive routes and which also may provide the sole clinically effective way to orally administer HA when other routes (e.g., injection) are not possible.

Another benefit is that embodiments of the present invention, with its high dose of Glucosamine sulfate, Hyaluronic acid, and Chondroitin sulfate, appears to have a synergistic effect which hastens the clinical response.

One further embodiment of the present invention is a unique formulation that combines Glucosamine sulfate, Chondroitin suifate, and Hyaluronic acid into a paste formulation for direct oral administration or top dressing feed. This is the only product available which combines these three substances which are critical for cartilage metabolism 10 Glucosamine Sulfate; and production of synovial fluid. Also, this embodiment is the only oral paste formulation available for any one of these supplements. Early clinical trials have shown that when the three products are combined, they have a synergistic effect. The clinical effects have been impressive. Data has shown a 15 quicker clinical response when GS, CS, and HA are combined than when they are used individually. Conditions in which embodiments of the present invention would be beneficial:

- 1) Osteoarthritis
- 2) Joint effusion
- 3) Joint inflammation and pain
- 4) Post operative arthroscopic surgery
- 5) Restoring proper joint function
- 6) Promote metabolic activity of chondrocytes (cartilage producing cells)
- 7) Inhibit enzymes that degrade cartilage
- 8) Stimulate the production of Hyaluronic acid.
- Embodiments of the present invention possess the following advantages:
 - 1) Only paste formulation
- 2) Only combination of GS, CS, HA in a paste formula-
- 3) Only oral paste form of Glucosamine
- 4) Only oral paste form of Chondroitin
- 5) Only oral paste form of Hyaluronic acid
- Only oral paste in a molasses flavored base
- 7) Only oral gel in apple flavored carboxymethylcellulose

One embodiment of the present invention possesses a molasses flavor. Other flavors would include apple, cherry, and any other palatable flavor. One embodiment of the present invention comprises the

following:

| | Wt % | |
|-------------------------|-------|--|
| Glucosamine sulfate | 46.03 | |
| Chandroitia aulfate | 4,60 | |
| Sodium Hysturosate | 0.18 | |
| Manaanese sulfate | 0.18 | |
| Powdered sugar | 8.70 | |
| Xanthan gum | 0.10 | |
| Mulasses | 25.00 | |
| Water | 14.00 | |
| Glycerine | 0.70 | |
| Com Starck | 0.30 | |
| Scolum Benzoate | 0.50 | |

Embodiments of the present invention in a paste formulation has many advantages. When adding to feed, the formulation will stick to grain to insure total consumption. Embodiments of the paste formulation can be given orally (direct administration) or added to feed-depending on 65 management of animals (e.g., whether turned out in field vs. stall confinement). Other advantages include the following:

- 1) Better absorption with liquids
- 2) Molasses flavored paste--more palatable
- 3) Apple flavored gel-more palatable
- 4) Sticky consistency---animal cannot spit product from mouth which insures total dose
- Syringe dose insures more accurate dose.
- Brown sugar included—more palatable
- Effects of GS vs CS:
- - 1) Enhances chondrocyte synthesis
 - 2) Enhances synthesis of hyaluronic acid
- 3) Reduces joint pain
- 4) Reduces synovitis
- Chondroitin Sulfate:
- 1) Also helps with chondrocyte synthesis
- 2) CS has been found to inhibit degradative enzymes in cartilage
- 20 3) CS strengthens and enhances vessels that feed joints or supply them with nutrients by reducing arterial plaque and clear cholesterol deposits.
 - Reduces joint pain and improves joint mobility.

5) Reduces synovitis associated with joint arthritis. Neither GS or CS fulfills the quest for the ideal chondroprotective/restorative agent separately but when combined they appear to provide the necessary components for the health and wellbeing of the joint. Hyaluronic acid complements the combination by helping to restore the HA levels needed for joint health and lubrication which are decreased when synovitis is present.

Hyaluronic acid is a glycosaminoglycan. Other glycosaminoglycans are Chondroitin sulfate, Heparin sulfate, and Dermatan sulfate. The most abundant GAG is Chondroitin sulfate. The three related GAGs have been found to be absorbed orally. Because of their chemical similarities and the clinical reports of improvement of synovitis, HA has a synergistic effect with GS and CS when given orally. This 49 effect is observed as a more rapid clinical response than when GS and CS are given individually.

Clinically, responses are seen in 7 to 10 days vs three to four weeks or not at all when GS and CS are given without HA. Therefore, we have seen a dramatic decrease in syno-45 vitis when HA is combined with GS and CS. This leads us to conclude that HA is absorbed orally and effective either alone or in combination with GS and CS. Therefore, an additional embodiment of the invention comprises a composition including HA and any acceptable carrier, such as the paste formulation disclosed herein and any other liquid, powder, get or similar type carrier.

Another embodiment of the invention includes a paste formulation containing the active component isoxuprine. Isoxuprine is a vasodilator and is utilized in treatment of many afflictions including the treatment of navicular disease. One effect of isoxuprine is that it stimulates the vasodilator nerves, such as the vaso-inhibitory and vasohypotonic nerves, and causes dilation or relaxation of the blood vessels. Administration of isoxuprine to a patient, such as an animal, in the form of a paste is beneficial to ensure adequate administration.

The present invention is illustrated by the following Examples, but should not be construed to be limited thereto. In the Examples, "part" and "%" are all part by weight or % by weight unless specified otherwise. Examples 1-14 are paste compositions of the invention.

| EXAMPLE 1 | | | Moisses Water DI | 23.5 |
|--|---------------|-----|---|--------------|
| Component | W: % | 5 | | |
| Sodium Hyalurosate | 0.144 | | TOTAL | 100 |
| Powdered Sugar 10X | 60.144 | | EXAMPLE 6 | |
| Glycerine | 0.7 | | | |
| Xanthan Gum | 0.2 | | Component | Wt % |
| Sodium Benzonte | 0.7 | 10 | Chondroitin Sutfate | 4 |
| Citric Acid Anhydrous Molasses | 23.5 | | Sodium Hyaleronate | 0.144 |
| Witter DI | 14.4 | | Manganese Sulfate | 0.144 |
| | | | Powdered Sugar 10X | 56 |
| TOTAL | 103 | | Glycerine | 0.7 |
| | | 15 | Xasthau Gum Sodium Benzoste | 0.2 0.7 |
| EXAMPLE 2 | - | | Citric Acid Anhydrous | 0.2 |
| Component | W: % | | Molaeses | 23.5 |
| | | | Water DI | 14.4 |
| Chondroitia Sulfate | 4 | | | 100 |
| Sodium Hyaluronate | 0.344 | 20 | TOTAL | 100 |
| Powdered Sugar 10X Giveerine | 50.144 0.7 | | EXAMPLE 7 | |
| Xanthan Gum | 0.2 | | | • |
| Sodium Benzoate | 6.7 | | Component | W: % |
| Citric Acid Anhydrous | 0.2 | | | |
| Molassas | 29.5 | 25 | Glucosamine Sulfate | 36 4 |
| Water DI | 14.4 | 2.3 | Chondroitin Sulfate Sodhum Hweluronate | 0.144 |
| | 100 | | Manganese Sulfite | 0.144 |
| TOTAL | 100 | | Powdered Sugar 10X | 20 |
| EXAMPLE 3 | | | Glycerins | 0.7 |
| EAAMFACES | - | | Xanthau Gum | 0.2 |
| Component | Wt % | .30 | Sodium Benzosse | 0.7 |
| Composition | | | Citric Acid Anhydrous Molusses | 0.2 23.5 |
| Giucosamine Sulfate | 40,144 | | Water DI | 14.4 |
| Sodium Hysturonate | 0.144 | | Pater Ex | |
| Powdered Sugar 10X | 20 | | TOTAL | 180 |
| Glycerine | 9.7 | 35 | | |
| Xanthan Gum | 0.2 | | EXAMPLE 8 | _ |
| Sodium Benzoste Citric Acid Anhydrous | 0.7 0.2 | | | Wt % |
| Molauses | 23.5 | | Component | A41.10 |
| Water DI | 14.4 | | Glucosamine Sulfate | 35 |
| Training to | | 40 | Canndroitin Sulfate | 4 |
| TOTAL | 300 | 40 | Sodium Hyaluronate | 0.144 |
| | | | Manganese Sulfate | 0.144 |
| EXAMPLE 4 | _ | | Vitamin C Powdered Sugar 10X | 20 |
| | | | Giverine | 6.7 |
| Component | Wt % | | Xanthan Gusa | 0.2 |
| Glucusamine Sulfate | 36.144 | 45 | Sodinm Benesate | 0.7 |
| Chondroitin Sulfate | 30.144 | | Citric Acid Anhydrous | 0.2 23.5 |
| Sodium Hyduronate | 0.144 | | Molasses Water DI | 23.5 14.4 |
| Powdered Sugar 10X | 20 | | WRIGT DI | 24.4 |
| Glycerine | 0.7 | | TOTAL | 160 |
| Xanshan Gutti | 9.2 | 50 | | |
| Sodium Benzonte | 0.7 | | EXAMPLE 9 | _ |
| Citrie Acid Anhydrous | 0.2 | | | 200 - |
| Molasses | 23.5 | | Consponent | Wt % |
| Water DI | 14.4 | | Glucosamiae Sulfate | 36 |
| TOTAL | 100 | 55 | Choaciroitia Sulfate | 4 |
| COUNT | 2007 | | Sociem Hysluronate | 0.144 |
| EXAMPLE 5 | | | Manganese Sulfate | 0.144 |
| Erwann Late | | | Vitamin D | 200 1 |
| Сотронен | Wt % | | Powdered Sugar 10X | 20 |
| | | | Glyceriae | 0.7 |
| Giucosamine Suifata | 36 | 66 | Xanthas Gum | 0,2 |
| Sodium Hyalurocate | 0.144 | | Sodium Benzoste | 0.7 |
| Manganese Sulfate | 0.144 | | Citric Acid Anhydrous | 0.2 |
| Powdered Sugar 10X | 24 | | Molasses | |
| Olycerine | 0.7 | | Water DI | 14.4 |
| Xanthan Gum Sodjum Benzoete | 0.2 6.7 | 6.5 | TOTAL. | 100 |
| | | | | |

| -continued | | | -continued | | |
|--|--|------------|--|---|--|
| EXAMPLE 19 | | | EXAMPLE 14 | | |
| Component | W1 % | 5 | Component | Wt % | |
| Glacosamine Suifate | 36 | _ | Glucosamine Sulfate | 46.93 | |
| | 4 | | Chondroitiu Sulfate | 4.60 | |
| Chondroitis Sulfate | 0,144 | | Sodism Hysluronate | 0.18 | |
| Sodium Hyalurenate | 0.144 | | Manganese Sulfate | 0.18 | |
| Manganese Sulfate | | 10 | Powdered Sugar 10X | 8.70 | |
| Buprofen | 200 mg | | Glycerine | 0.7 | |
| Powdered Sugar 10X | 20 | | Xanthan Gum | 0.16 | |
| Glycarine | 0.7 | | Sodium Benzoste | 0.50 | |
| Xanthan Gum | 0.2 | | Com Starch | 0.30 | |
| Sodium Benzoste | 0.7 | | Molasses | 25.00 | |
| Citric Acid Auhydrous | 0.2 | 15 | Water DI | 14.0 | |
| Molasses | 23.5 | | | | |
| Water DI | 14.4 | | TOTAL | 100 | |
| TOTAL | 100 | | | | |
| EXAME | 'LE 11 | 20 | | | |
| Component | W: % | | | | |
| Glucosamine Sulfate | 36 | | EXAMPLE | 15 | |
| Chandroitin Suifate | 30 A | | | | |
| Sodium Hvaluronate | 0.144 | 25 | | | |
| Manganese Sulfate | 0.144 | 23 | | | |
| | 200 mg | | | | |
| Erythromycia | 200 mg | 1 | he following Example is direct | ed to a gel of HA usin | |
| Powdered Sugar 10X | 0.7 | CM | C as the gelling agent. | | |
| Giyosrine | | · · · · | C ID the Sevent allent | | |
| Xanthan Gum | 0.2 | ** | | | |
| Sodium Benzoate | 0.7 | 30 | | | |
| Citric Acid Anhydrous | 0.2 | | | | |
| Molasses | 23.5 | | Component | W: % | |
| Water DI | 14.4 | | Sodium Hyaluronate | 1.90 | |
| TOTAL | 100 | 35 | Sodium Carboxymethyl cellulose | 1.50 | |
| EXAM | PLE 12 | | Propylene glycol Sodium Benzoste | 1.20 0.50 | |
| | | | | | |
| Component | W: % | | Citrie Acid Apple Player | 0.30 1.5 | |
| | | | Citric Acid Apple Plavor Water Di | 0.30 1.5 94.5 | |
| Glucosamine Sulfate | 36 | 40 | Apple Plavor Water Di | 1.S 94.5 | |
| Glucosamine Sulfate Chondroitin Sulfate | 36 4 | 40 | Apple Plavor | 1.5 | |
| Glucosamine Sulfate Chondroitin Sulfate Sodium Hyaluronate | 36 4 0,144 | 40 | Apple Plavor Water Di | 1.S 94.5 | |
| Glucosamine Sulfate Chondroitin Sulfate Sodium Hyaluronate Manganese Sulfate | 36 4 0,144 6,144 | 40 | Apple Plavor Water Di | 1.S 94.5 | |
| Glucosamine Sulfate Chondroitin Sulfate Sodium Hyaluromate Manganese Sulfate Isomprine | 36 4 0,144 3,144 190 mg | 40 | Apple Plavor Water Di | 1.S 94.5 | |
| Glucosamins Sulfate Chondroltin Sulfate Sodium Hyahrronate Manganese Sulfate Isoxuprine Powdered Sugar 10X | 36 4 0,144 9,144 190 mg 20 | 40 | Apple Plavor Water Di | 1.5 94.5 | |
| Glucosamine Sulfate Chendroitin Sulfate Sodium Hyhrmonate Manganese Sulfate Isomprine Powdered Sugar 10X Glyverine | 36 4 0.144 0.144 190 mg 20 0.7 | | Apple Plavor Water Di | 1.5 94.5 | |
| Otucoasmine Sulfate Chondroitin Sulfate Sodium Hyahurosate Manganese Sulfate Isomogrine Powdered Sugar 10X Giyeerine Xasahan Gum | 36 4 0,144 0,144 190 mg 20 0,7 | 46 | Apple Plavor Water Dt TOTAL | 1.5 94.5 100 | |
| Glucosamine Sulfate Chondroitin Sulfate Sodium Hyshuronate Manganese Sulfate Isocusprine Powdered Sugar 10X Glycerine Xasshan Gum Sodium Benzoate | 36 4 0.144 9.144 190 ssg 20 0.7 0.2 0.7 | | Apple Plavor Water Di | 1.5 94.5 190 | |
| Glucosamine Sulfate Chondroith Sulfate Sodium Hyalurosase Manganese Sulfate Bocupirise Powdered Sugar 10X Glycetine Xanshan Gum Sodium Benzoste Citric Acid Antipidrous | 36 4 0.144 0.144 100 mg 20 0.7 0.2 0.7 | | Apple Plavor Water Dt TOTAL | 1.5 94.5 100 | |
| Chucosamine Sulfate Chondroitin Sulfate Condimit Sulfate Sodium Hyhatronate Manganese Sulfate Isocouprine Powdered Sugar 10X Glyestine Xenthan Gum Sodium Bezusste Citric Acid Anbydrous Molasses | 36 4 0.144 0.144 100 mg 20 0.7 0.2 0.7 0.2 2.3.5 | | Apple Plavor Water Dt TOTAL | 1.5 94.5 100 | |
| Glucosamine Sulfate Chondroith Sulfate Sodium Hyalurosase Manganese Sulfate Bocupirise Powdered Sugar 10X Glycetine Xanshan Gum Sodium Benzoste Citric Acid Antipidross | 36 4 0.144 0.144 100 mg 20 0.7 0.2 0.7 | | Apple Plavor Water Dt TOTAL | 1.5 94.5 100 | |
| Chucosamine Sulfate Chondroitin Sulfate Condimit Sulfate Sodium Hyhatronate Manganese Sulfate Isocouprine Powdered Sugar 10X Glyestine Xenthan Gum Sodium Bezusste Citric Acid Anbydrous Molasses | 36 4 0.144 0.144 100 mg 20 0.7 0.2 0.7 0.2 2.3.5 | 45 50 T | Apple Flavor Water DI TOTAL EXAMPLE the following Example is direct | 1.5 94.5 100 | |
| Chucosamine Sulfate Chondroitin Sulfate Condim Phylatronate Sodium Hylatronate Manganese Sulfate Isocouprine Powdered Sugar 10X Cityestine Xanthan Gum Sodium Bezusate Citric Acid Anbydrous Molasses Water DI | 36 4 0.144 0.144 1900 mg 20 0.7 0.2 0.7 0.2 23.5 14.4 | 45 50 T | Apple Flavor Water DI TOTAL EXAMPLE | 1.5 94.5 100 | |
| Glucesamine Sulfate Chondrottin Sulfate Sodium Hybatronate Manganere Sulfate Manganere Sulfate Providered Sugar 10X Glyperine Fantana Gum Sodium Benzonate Cluic Acid Anhydrous Mobasee Water DY TOTAL | 36 4 0.144 0.144 1900 mg 20 0.7 0.2 0.7 0.2 23.5 14.4 | 45 50 T | Apple Flavor Water DI TOTAL EXAMPLE the following Example is direct | 1.5 94.5 100 | |
| Ohicosamins Solfate Controloid Solfate Controloid Solfate Solidin Hybranese Mangaeret Solfate Boxoppites Glyschie Glyschie August 10X Glyschie August 10X Glyschie August 10X Glyschie August 10X Moharet Water DI TOTAL EXAMI Component | 36 4 0.144 0.144 190 mg 0 0 0,7 0,2 0,7 0,2 0,7 0,2 1,3 1,4 1,4 1,00 | 45 50 T | Apple Flavor Water DI TOTAL EXAMPLE the following Example is direct | 1.5 94.5 100 | |
| Olucosamina Solfate Chondrolin Sulfate Chondrolin Sulfate Solfum Hybraneule Experiment Sulfate Longrice Fooderad Sugar 10X Olycerine Xesthan Gum Soldium Benzoule Chirk And Abulgfrout Water DX TOTAL EXAMI Component Gleccusmine Sulfate Gleccusmine Sulfate | 36 4 0.144 0.144 1900 mg 20 07 0.2 0.7 0.2 23.5 14.4 100 | 45 50 T | Apple Flavor Whate DI TOTAL EXAMPLE The following Example is directed in the condition of | 1.5 94.5 100 16 ted to a gel of HA an s the gelling agent. W: © | |
| Olucosanias Solfas Chondrolin Solfas Chondrolin Solfas Mesgacere Solfan Incomprise Foodered Sugar 10X Giyestia Solfan Bezzote Ciric Acid Arbydrous Moharer Viter DI TOTAL DXAMI Composeut Glecusanias Solfas Solfan Biptomose | 36 4 3.144 3.144 3.100 mg 20 2.7 2.2 2.3 5.14.4 3.100 3.144 3.100 3.144 | 45 50 T | Apple Flavor Water DI TOTAL EXAMPLE The following Example is direct adrollin sulphate using CMC a Component Sodium Hymbronate | 1.5 04.5 100 100 100 100 100 100 100 100 100 10 | |
| Ohucosamins Solfate Chondrolin Sulfate Chondrolin Sulfate Solfum Hybraneade Managoria English English English English English English English English Solfum Berzoste Chir Acid Anaptrous Molasses Where Dt TOTAL EXAMI Component Component Component Solfum Berzoste Solfum Bybromies Solfum Bybromies Buprofice | 36 4 4 4 0.144 1.144 1.144 1.144 1.144 1.144 1.144 1.144 1.144 1.144 1.144 1.144 1.144 1.144 1.144 1.144 1.144 1.144 1.144 1.10 0.144 1.14 | 45 50 T | Apple Flavor Water DI TOTAL EXAMPLE Example is direct direction sulphate using CMC a Component Sodium Hymbronate Chenchoits Sulphate | 1.5 94.5 100 16 16 16 16 17 18 18 18 18 18 18 18 18 18 18 18 18 18 | |
| Olucosamina Solfate Chondrolin Sulfate Chondrolin Sulfate Chondrolin Sulfate Managaree Sulfate Incomprise Proutfered Sugar 10X Olyserine Xintha Gurzone Ciric Acid Arbylrous Molareex Water Di TOTAL EXAMI Camponent Glocomaine Sulfate Solomin Sulfate Solomin Sulfate Dopprise Proutfered Sugar 10X | 36 4 0.144 0.144 0.140 100 mg 00 0.7 0.2 0.2 0.2 2.35 14.4 100 PLE 13 Wi % | 45 50 T | Apple Flavor Water DI TOTAL EXAMPLE Total EXAMPLE Total Example is direct adroitin sulphate using CMC a Composer Composer Condition Sulphate Condition Conditi | 1.5 94.5 100 16 ted to a gel of HA at the gelling agent. W: % | |
| Ohucosamins Solfate Constroids Sulfate Constroids Sulfate Solfin Highwareale Manganet Solfate Fowdered Sugar 10X Olynetine Xustakan Gurn Sodium Benzoste Ciriz Andri Anhydrous Molosteet White DY TOTAL EDXAMI Component Glovcumnine Sulfate Solfate Boundered Fowdered Sugar 10X Olynetine Fowdered Sugar 10X Olynetine | 36 4 0.144 0.144 1.190 mg 0.0 7 0.2 0.7 0.2 2.5 1.44 1.00 Wt % 40.144 0.144 0.144 0.044 20 0.7 | 50 T cho | Apple Flavor Water DI TOTAL EXAMPLE EXAMPLE the following Example is direct adroitin sulphate using CMC a Component Sodium Hyularcaste Chesheduin Sulphate Chesheduin Sulphate Collabora Collabora Collabora Collabora | 1.5 94.5 100 16 16 tied to a gel of HA at the gelling agent. Wh % | |
| Olucosamina Solfate Chontrolish Subitate Solfant Phylamente Solfant Phylamente Solfant Phylamente Description Examina Solfant EXAMi Champonett Ghorcusmine Sulfate Solfant Hylamrosse Desprinte Solfant Solfan | 36 4 0.144 0.144 0.144 0.100 mg 0.0,7 0.2 0.7 0.2 0.2,3.5 1.4.4 100 Vit % 40.144 0.144 800 mg 20 7 0.7 0.2 | 45 50 T | Apple Flavor Water DI TOTAL EXAMPLE EXAMPLE The following Example is direct adroitin sulphate using CMC a Component Sodium Hymbronate Considering Sulphate Sodium Cutocoynethyl Sodium Cutocoynethyl Popylene glysol | 1.5 94.5 100 16 ted to a gel of HA at s the gelling agent. Wh % 400 1.00 | |
| Olucosanias Solfas Chondrolin Solfas Chondrolin Solfas Chondrolin Solfas Magazere Solfan Incomprise Foodrard Sugar 10X Giyestia Solfan Solfan Bezzote Ciric Acid Arbydrous Moharer Water DI TOTAL DEAMI Composeus Gleccusmine Sulfas Solfan Biphromate Buprifee Powderd Sugar 10X Xanhias Gun Solfan Bezzote Solfan Biphromate Buprifee Solfan Biphromate Buprifee Solfan Biphromate Bi | 36 4 0.144 0.144 0.100 mg 0.0 7 0.0 2 0.7 0.2 23.5 14.4 100 PLE 13 W1 % 40.144 800 mg 20 0.0 2 0.144 | 50 T cho | Apple Flavor Water DI TOTAL EXAMPLE TOTAL EXAMPLE Total EXAMPLE Total EXAMPLE Total Component Sodium Hymbronate Chond-chin Sulphate Sodium Chrowymethyl cellabore Sodium Exchowymethyl cellabore Sodium Explore Exp | 1.5 94.5 100 166 teet to a gel of HA as the gelling agent. W: * 1.00 4.00 1.00 1.00 0.36 | |
| Olucosamina Solfate Chondrolin Sulfate Chondrolin Sulfate Soulim Hybrimenia Experimental Sulfate Experimental Sulfate Experimental Sulfate Soulim Benzoste Ciric Acid Abulgirous Water DX TCTAL EXAMI Component General Sulfate Sodium Hybrimenia Sulfate | 36 4 4 4 1.44 1.44 1.44 1.45 1.45 1.45 1.4 | 50 T cho | Apple Flavor Water DI TOTAL EXAMPLE Example is direct direction sulphate using CMC a Compount Sodium Upharonate Condoids Sulphate Sodium Carbovymethyl collabore Propylene glycol Curic Acid Ciric Acid | 1.5 94.5 100 166 167 168 168 169 169 169 169 169 169 169 169 169 169 | |
| Olucosamina Solfate Chondrolin Solfate Chondrolin Solfate Chondrolin Solfate Magazere Solfate Incomprise Foodered Sugar 10X Giyasthe Xustaten sun Citic Acid Ambydrous Molarere Water DI TOTAL EXAMI Component Girc.camine Solfate Solfate Haphyrouse Buprofice Foodered Sugar 10X Giyasthe Chira Chi | 36 4 0.144 0.144 0.100 mg 0.0 0.7 0.2 0.2 2.8.5 14.4 100 PLE 13 Wi % 40.144 | 50 T cho | Apple Flavor Water DI TOTAL EXAMPLE EXAMPLE Total EXAMPLE Component Sodium Hyularcouste Chondedinia Sulphate Solium Hyularcouste Chondedinia Sulphate Solium Hyularcouste Chondedinia Sulphate Solium Bazzonie Apple Flavor Apple Flavor | 1.5 94.5 100 166 167 168 168 168 168 168 168 168 168 168 168 | |
| Olucosamina Solfate Chondrolin Sulfate Chondrolin Sulfate Soulim Hybrimenia Experimental Sulfate Experimental Sulfate Experimental Sulfate Soulim Benzoste Ciric Acid Abulgirous Water DX TCTAL EXAMI Component General Sulfate Sodium Hybrimenia Sulfate | 36 4 4 4 1.44 1.44 1.44 1.45 1.45 1.45 1.4 | 50 T cho | Apple Flavor Water DI TOTAL EXAMPLE Example is direct direction sulphate using CMC a Compount Sodium Upharonate Condoids Sulphate Sodium Carbovymethyl collabore Propylene glycol Curic Acid Ciric Acid | 1.5 94.5 100 166 167 167 167 167 167 167 167 167 167 | |

EXAMPLE 16

Hard gelatin capsules are prepared using the following ingredients

| Component | Amount mg | |
|--------------------|-----------|--|
| Sodium Hyaluronste | 100.00 | |
| Starch dried | 200.08 | |
| Magnosium sicurate | 10.00 | |
| TOTAL | 310.60 | |

EXAMPLE 17

Hard gelatin capsules are prepared using the following ingredients

| | | 20 |
|----------------|--|--|
| nent | Amoust mg | |
| Hyekironate | 100.00 | |
| oitin sulphate | 209.00 | |
| dried | 200.00 | |
| sium steenste | 10.00 | 25 |
| | 510.00 | |
| | ment h Hyshuronate oitia sulphate dried sium steamte | r Hyshirenste 150.00 oitis supphate 200.00 dried 200.00 sium sterrate 10.00 |

The above ingredients are mixed and filled into hard gelatin capsules in 510 mg quantities.

EXAMPLE 18

Hard gelatin capsules are prepared using the following ingredients

| Component | Amount ing | |
|----------------------------|------------|----|
| Sodium Hysiuronate | 100.00 | _ |
| Microcrystalline cullulose | 400.00 | 40 |
| Silicon Dioxide, fumed | 10.00 | |
| Steanic Acid | 5.00 | |
| TOTAL | 310.00 | |

The components are blended and compressed to form tablets each weighing 665 mg.

While the invention has been described in conjunction with specific embodiments thereof, it is evident that many alternatives, modifications, and variations will be apparent 50 to those skilled in the art in light of the foregoing description. Accordingly, it is intended to embrace all such alternatives, modifications, and variations which fall within the spirit and broad scope of the invention.

1. An orally administrable Chondroprotective/Restorative composition in gel or paste form for administration to a mammal comprising an effective amount Hyaluronic Acid or its pharmaceutically acceptable salts an a pharmaceutically acceptable gelling or pasting agent capable of forming a gel 66 or a paste selected from the group consisting of hydroxypropyl methyl cellulose, hydroxymethyl cellulose, methyl cellulose, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, cellulose acetate, ethyl cellulose, methyl hydroxy ethyl cellulose, hydroxy ethyl cellulose, cellulose gum 65 carboxymethylceliulose, sodium carboxymethylcellulose and molasses.

- 2. The Chondroprotective/Restorative composition of claim 1 further including nutritionally effective amounts of a supplement selected from the group consisting of vitamin A. D and E. ascorbic acid, biotin, panthothenic, choline, niacin, pyridoxine, riboflavin, thiamine, calcium, phosphorus, NaCI, copper, iron, manganese, iodine, zinc and combinations thereof.
- 3. An orally administrable Chondroprotective/Restorative composition comprising:
- (a) an effective amount of Glucosamine sulfate;
- (b) an effective amount Hyaluronic Acid or pharmaceutically acceptable salts thereof; and
- (c) a pharmaceutically acceptable gelling or pasting agent capable of forming a gel or a paste selected from the group consisting of hydroxypropyl methyl cellulose, hydroxymethyl cellulose, methyl cellulose, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, cellulose acetate, ethyl cellulose, methyl hydroxy ethyl cellulose, hydroxy ethyl cellulose, cellulose gum carboxymethylcellulose, sodium carboxymethylcellulose and molasses.
- 4. The Chondroprotective/Restorative composition of claim 3 further including nutritionally effective amounts of a supplement selected from the group consisting of vitamin A, D and E, ascorbic acid, biotin, panthothenic, choline, niacin, pyridoxine, riboflavin, thiamine, calcium, phosphorus, NaCl, copper, iron, manganese, iodine, zinc and combinations thereof.
- 5. An orally administrable Chondroprotective/Restorative composition comprising
- (a) an effective amount of Chondroitin sulfate;
- (b) an effective amount of Hyaluronic Acid or pharmaceutically acceptable salts thereof; and
- (c) a pharmaceutically acceptable gelling or pasting agent capable of forming a gel or a paste selected from the group consisting of hydroxypropyl methyl cellulose, hydroxymethyl cellulose, methyl cellulose, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, celbilose acetate, ethyl cellulose, methyl bydroxy ethyl cellulose, hydroxy ethyl cellulose, cellulose gum carboxymethylcellulose, sodium carboxymethylcellulose and molasses.
- 6. The Chondroprotective/Restorative composition of claim 5 further including nutritionally effective amounts of a supplement selected from the group consisting of vitamin A, D and E, ascorbic acid, biotin, panthothenic, choline, niacin, pyridoxine, riboflavin, thiamine, calcium, phosphorus, NaCI, copper, iron, manganese, iodine, zinc and combinations thereof.
- 7. An orally administrable Chondroprotective/Restorative composition comprising
 - (a) an effective amount of Glucosamine sulfate;
 - (b) an effective amount of Chondroitin sulfate:
- (c) an effective amount of Hyaluronic Acid or pharmaccutically acceptable salts thereof; and
- (d) a pharmaceutically acceptable gelling or pasting agent capable of forming a gel or a paste selected from the group consisting of hydroxypropyl methyl cellulose, hydroxymethyl cellulose, methyl cellulose, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, celbulose acciate, ethyl cellulose, methyl hydroxy ethyl cellulose, hydroxy ethyl cellulose, cellulose gum carboxymethylcellulose, sodium carboxymethylcellulose and molasses.
- 8. The Chondroprotective/Restorative composition of claim 7 further including nutritionally effective amounts of

a supplement selected from the group consisting of vitamin A, D and E, ascorbic acid, biotin, panthothenic, choline, niacin, pyridoxine, riboflavin, thiamine, calcium, phosphorus, NaCl copper, iron, manganese, iodine, zinc and combinations thereof

9. A therapeutic and Chondroprotective/Restorative composition in gel form for oral administration comprising: (a) an effective amount of hyaluronic Hyaluronic Acid or

its pharmaceutically acceptable salts;

(b) an effective amount of a therapeutic drug; and

(c) a pharmaceutically acceptable gelling or pasting agent capable of forming a gel or a paste selected from the group consisting of hydroxypropyl methyl cellulose, hydroxymethyl cellulose, methyl cellulose, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, cel- 15 lulose acetate, ethyl cellulose, methyl hydroxy ethyl cellulose, hydroxy ethyl cellulose, cellulose gum carboxymethylcellulose, sodium carboxymethylcellulose and molasses.

10. The therapeutic and Chondroprotective/Restorative 20 composition of claim 9 wherein said therapeutic drug is selected from the group consisting of acetaminophen, acetic acid, acetylsalicylic acid, buffered acetylsalicylic acid, albuterol, albuterol sulfate, ethanol isopropanol, allantoin, aloe, aluminum acetate, aluminum carbonate, aluminum 25 chlorohydrate, aluminum hydroxide, alprozolam, amino acids, aminobenzoic acid, amoxicillin, ampicillin, amsacrine, amsalog, anethole, aspartame, atenolol, bacitracin, balsam peru, beclomethasone dipropionate, peroxide, biotin, bisacodyl, bornyl acetate, bromopheniramine maleate, buspirone, caffeine, calamine, calcium, calcium carbonate, calcium casinate, calcium hydroxide, camphor, captopril, cascara sagrada, castor oil, cetylalcohol, cetylpyridinium chloride, chelated minerals, chloramphenicol, chlorevelizine hydrochloride chlorhexidine gluconate, chloroxylenol, chloropentostatin, chlorpheniramine maleate, cholestyramine resin, choline bitartrate, cimetidine hydrochloride, cinnamedrine hydrochloride, 40 undecylenate citalopram, citric acid, Cleabuterol, cocoa butter, cod liver oil, codeine and codeine phosphate, clonidine, clonidine hydrochloride, clorfibrate, ciprofloxacin HCl. evanocobalamin, cyclizine hydrochloride, DMSO, danthron, Dantrium, dexamethazone, dexbrompheniranime 45 maleate, dextromethorphan hydrobromide, diazapam, dibucaine, diclofenac sodium, digoxin, diltiazem, dimethicone, dioxybenzone, diphenhydramine citrate, diphenhydramine hydrochloride, docusate calicum, docusate potassium, docusate sodium, doxycycline hyclate, 50 doxylamine succinate, efaroxan, enalapril, enoxacin, erythromycin, estropipate, ethinyl estradiol, ephedrine, eninephrine bitartrate, erythropoietin, eucalyptol, ferrous fumarate, ferrous gluconate, ferrous sulfate, folic acid, fosphenytoin, Flunixin Meglumine, fluoxetine HCl, 55 furosemide, gabapentan, gentamicia, Gentocia sulfate, gemfibrozil, glipizide, glycerin, glyceryl stearate, griscofulvin, guaifenesin, hexylresorcinol, hydrochlorothiaxide, hydrocodone bitartrate, hydrocortisone, hydrocortisone acetate, 8-hydroxyquinoline 60 sulfate, ibuprofen, indomethacin, inositol, insulin, iodine, inecac, iron, isoxicam, Isoxuprine, ketamine, Ketofin, koalin, lactic acid, lanolin, lecithin, lidocaine, lidocaine hydrochloride, lifinopril, liotrix, lovastatin, MSM (methylsulfonylmethane), magnesium carbonate, magne- 65 sium hydroxide, magnesium salicylate, magnesium trisilocate, mefenamic acid, meclofenanic acid, meclofe-

namate sodium, medroxyprogesterone acctate, methenamine, mandelate, Methocarbamol, menthol, meperidine hydrochloride, metaproterenol sulfato, methyl nicotinate, methyl salicylate, methylcollulose, methauximide, metromidazole, metromidazole hydrochloride, metoprolol tartrate, miconazole nitrate, mineral oil, minoxidil, morphine, naproxen, naproxen sodium, nifedipine, neomycin sulfate, Neomycin-Bacitracin, niacin, niacinamide, nicotine, nicotinamide, nitroglycerin, nonexynol-9, perethindone, perethindone acetate, avstatin, octoxynol, octyl dimethyl PABA, octyl methoxycinnamate, omega-3 polyunsaturated fatty acids, omegrazole, oxolinic acid, oxybenzone, oxtriphylline, para-aminobenzoic acid (PABA), padimate O, paramethadione, Penicillin, pentastatin, peppermint oil, pentaerythriol tetranitrate, pentobarbital sodium, pheniramine malente, phenobarbital, phenol, phenolphthalein, phenybutazone phenylbutazone, phenylephrine hydrochloride, phenylpropanolamine, phenylpropanolamine hydrochloride, phenytoin, phenelzine sulfate, pinnenol, piroxicam, polymycin B sulfate, potassium chloride, potassium nitrate, prazepam, prednisone, preduisolone, procainamide hydrochloride, procaterol, propoxyphene, propoxyphene HCl, propoxyphene napsylate, pramiracetin, pramoxine, pramoxine hydrochloride, propronolol HCl pseudosphedrine hydrochloride, pseudoephedrine sulfate, pyridoxine, quinapril, quinidine gluconate, quinestrol, ralitoline, ranitadine, resorcinol, riboffavin, salicylic acid, sesame oil, benzocaine, benzoic acid, benzophenones, benzoyl 30 shark liver oil, simethicone, sodium bicarbonate, sodium citrate, sodium fluoride, sodium monofluorophosphate, Sulfa-drugs, sulfanethoxazole, sulfur, tacrine, tacrine HCl, theophylline, terfenidine, thioperidone, trimetrexate, triazolam, timolol maleate, tretinoin, tetracycline Cephalosporius, cefaclor, cefadoxil, cephalexiu, 35 hydrochloride, tolmetin, tolnaffate, trismcinolone, triclosan, triprolidine hydrochloride, undecylenic acid, vancomycin, verapamil HCl, vidaribine phosphate, vitamin A, vitamin B, vitamin C, vitamin D, vitamin E, vitamin K, witch hazel, xylometazoline hydrochloride zine, zine sulfate, and zine

11. An oral Chondroprotective/Restorative composition in paste from comprising:

(a) an effective amount of Hyaluronic Acid or its pharmaceutically acceptable salts; and

(b) a sufficient amount of molasses to make a paste. 12. The Chondroprotective/Restorative composition of

claim 11 further including glucosamine sulfate. 13. The Chondroprotective/Restorative composition of claim 12 further including nutritionally effective amounts of vitamins and minerals.

14. The Chondroprotective/Restorative of claim 11 further including chondroitin sulfate.

15. An orally administrable Chondroprotective/ Restorative composition in get form comprising:

(a) an effective amount of Hyahironic Acid or its pharmaceutically acceptable salts;

(b) water; and

(c) a sufficient amount of carboxymethylcellulose or its sodium salt to make a gel.

16. The Chondroprotective/Restorative composition of claim 15 further including glucosamine sulfate. 17. The Chondroprotective/Restorative composition of

claim 15 further including chondroitin sulfate. 18. The chondroprotective/Restorative composition of claim 15 further including nutritionally effective amounts of vitamins and minerals.

 The Chondroprotective/Restorative composition of claim 18 further including chondroitin sulfate.

20. A method of treating osteoarthritis, joint effusion, joint inflammation and pain, synovitis, lameness, post operative arthroscopic surgery, deterioration of proper joint function, 5 the reduction or inhibition of methodic activity of chondrocytes, the activity of enzymes that degrade cartilage, the reduction or inhibition of the production of Hyaluronic acid in a mammal, said method comprising orally administering to said mammal a therapeutically effective amount of 10 the composition of claim 1.

21. The method of claim 20 further including an effective amount of Glucosamine or its pharmaceutically acceptable salts.

22. The method of claim 21 wherein said pharmaceuti- 15 cally acceptable sait is glucosamine sulfate.

23. The method of claim 20 further including an effective amount of chondroitin or its pharmaceutically acceptable

alts.

24. The method of claim 23 wherein said pharmaceuti-

cally acceptable salt is chondroitin sulfate.

25. The method of claim 20 further including therapeutically effective amounts of glucosamine sulfate and chondroities.

droitin sulfate.

26. The method according to claim 20 wherein said

hyalaronic acid is uncrosslinked.
27. The method according to claim 26 wherein said

the range of 10 mg to 2000 mg.

28. The method according to claim 20 wherein said pharmaceutically acceptable salt is sodium hyaluronate.

* * * * *